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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

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EC – Bananas III	Appellate Body Report, *European Communities – Regime for the Importation, Sale and Distribution of Bananas*, WT/DS27/AB/R, adopted 25 September 1997, DSR 1997:II, 591
EC – Bananas III (Article 21.5 – EC)	Panel Report, *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Article 21.5 of the DSU by the European Communities*, WT/DS27/RW/EEC and Corr.1, 12 April 1999, unadopted, DSR 1999:II, 783
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EC – Commercial Vessels	Panel Report, *European Communities – Measures Affecting Trade in Commercial Vessels*, WT/DS301/R, adopted 20 June 2005
EC – Hormones	Appellate Body Report, *EC Measures Concerning Meat and Meat Products (Hormones)*, WT/DS26/AB/R, WT/DS48/AB/R, adopted 13 February 1998, DSR 1998:I, 135
EC – Hormones (Canada)	Panel Report, *EC Measures Concerning Meat and Meat Products (Hormones), Complaint by Canada*, WT/DS48/R/CAN, adopted 13 February 1998, as modified by Appellate Body Report, WT/DS26/AB/R, WT/DS48/AB/R, DSR 1998:II, 235
EC – Hormones (US)	Panel Report, *EC Measures Concerning Meat and Meat Products (Hormones), Complaint by the United States*, WT/DS26/R/USA, adopted 13 February 1998, as modified by Appellate Body Report, WT/DS26/AB/R, WT/DS48/AB/R, DSR 1998:III, 699
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Korea – Dairy	Panel Report, *Korea – Definitive Safeguard Measure on Imports of Certain Dairy Products*, WT/DS98/R and Corr.1, adopted 12 January 2000, as modified by Appellate Body Report, WT/DS98/AB/R, DSR 2000:I, 49
Korea – Procurement	Panel Report, *Korea – Measures Affecting Government Procurement*, WT/DS163/R, adopted 19 June 2000, DSR 2000:VIII, 3541
US – Carbon Steel	Appellate Body Report, *United States – Countervailing Duties on Certain Corrosion-Resistant Carbon Steel Flat Products from Germany*, WT/DS213/AB/R and Corr.1, adopted 19 December 2002, DSR 2002:IX, 3779

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US – Certain EC Products	Appellate Body Report, *United States – Import Measures on Certain Products from the European Communities*, WT/DS165/AB/R, adopted 10 January 2001, DSR 2001:I, 373
US – Certain EC Products	Panel Report, *United States – Import Measures on Certain Products from the European Communities*, WT/DS165/R and Add.1, adopted 10 January 2001, as modified by Appellate Body Report, WT/DS165/AB/R, DSR 2001:II, 413
US – FSC	Appellate Body Report, *United States – Tax Treatment for "Foreign Sales Corporations"*, WT/DS108/AB/R, adopted 20 March 2000, DSR 2000:III, 1619
US – FSC	Panel Report, *United States – Tax Treatment for "Foreign Sales Corporations"*, WT/DS108/R, adopted 20 March 2000, as modified by Appellate Body Report, WT/DS108/AB/R, DSR 2000:IV, 1675
US – Gambling	Appellate Body Report, *United States – Measures Affecting the Cross-Border Supply of Gambling and Betting Services*, WT/DS285/AB/R and Corr.1, adopted 20 April 2005, DSR 2005:XII, 5663
US – Gambling	Panel Report, *United States – Measures Affecting the Cross-Border Supply of Gambling and Betting Services*, WT/DS285/R, adopted 20 April 2005, as modified by Appellate Body Report, WT/DS285/AB/R, DSR 2005:XII, 5797
US – Hot-Rolled Steel	Appellate Body Report, *United States – Anti-Dumping Measures on Certain Hot-Rolled Steel Products from Japan*, WT/DS184/AB/R, adopted 23 August 2001, DSR 2001:X, 4697
US – Hot-Rolled Steel	Panel Report, *United States – Anti-Dumping Measures on Certain Hot-Rolled Steel Products from Japan*, WT/DS184/R, adopted 23 August 2001 modified by Appellate Body Report, WT/DS184/AB/R, DSR 2001:X, 4769
US – Line Pipe	Appellate Body Report, *United States – Definitive Safeguard Measures on Imports of Circular Welded Carbon Quality Line Pipe from Korea*, WT/DS202/AB/R, adopted 8 March 2002, DSR 2002:IV, 1403
US – Line Pipe	Panel Report, *United States – Definitive Safeguard Measures on Imports of Circular Welded Carbon Quality Line Pipe from Korea*, WT/DS202/R, adopted 8 March 2002, as modified by Appellate Body Report, WT/DS202/AB/R, DSR 2002:IV, 1473
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US – Offset Act (Byrd Amendment)	Panel Report, *United States – Continued Dumping and Subsidy Offset Act of 2000*, WT/DS217/R, WT/DS234/R, adopted 27 January 2003, as modified by Appellate Body Report, WT/DS217/AB/R, WT/DS234/AB/R, DSR 2003:II, 489
US – Section 211 Appropriations Act	Appellate Body Report, *United States – Section 211 Omnibus Appropriations Act of 1998*, WT/DS176/AB/R, adopted 1 February 2002, DSR 2002:II, 589
US – Section 211 Appropriations Act	Panel Report, *United States – Section 211 Omnibus Appropriations Act of 1998*, WT/DS176/R, adopted 1 February 2002, as modified by Appellate Body Report, WT/DS176/AB/R, DSR 2002:II, 683
US – Section 301 Trade Act	Panel Report, *United States – Sections 301-310 of the Trade Act of 1974*, WT/DS152/R, adopted 27 January 2000, DSR 2000:II, 815

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US – Shrimp	Appellate Body Report, *United States – Import Prohibition of Certain Shrimp and Shrimp Products*, WT/DS58/AB/R, adopted 6 November 1998, DSR 1998:VII, 2755
US – Shrimp	Panel Report, *United States – Import Prohibition of Certain Shrimp and Shrimp Products*, WT/DS58/R and Corr.1, adopted 6 November 1998, as modified by Appellate Body Report, WT/DS58/AB/R, DSR 1998:VII, 2821
US – Softwood Lumber VI	Panel Report, *United States – Investigation of the International Trade Commission in Softwood Lumber from Canada*, WT/DS277/R, adopted 26 April 2004, DSR 2004:VI, 2485
US – Upland Cotton	Appellate Body Report, *United States – Subsidies on Upland Cotton*, WT/DS267/AB/R, adopted 21 March 2005
US – Upland Cotton	Panel Report, *United States – Subsidies on Upland Cotton*, WT/DS267/R, and Corr.1, adopted 21 March 2005, as modified by Appellate Body Report, WT/DS267/AB/R
US – Wool Shirts and Blouses	Appellate Body Report, *United States – Measure Affecting Imports of Woven Wool Shirts and Blouses from India*, WT/DS33/AB/R and Corr.1, adopted 23 May 1997, DSR 1997:I, 323
US – Wool Shirts and Blouses	Panel Report, *United States – Measure Affecting Imports of Woven Wool Shirts and Blouses from India*, WT/DS33/R, adopted 23 May 1997, upheld by Appellate Body Report, WT/DS33/AB/R, DSR 1997:I, 343

I. INTRODUCTION

A. REQUEST FOR CONSULTATIONS AND REQUEST FOR THE ESTABLISHMENT OF A PANEL

1.1 On 8 November 2004, the European Communities requested consultations with Canada pursuant to Article XXII:1 of the General Agreement on Tariffs and Trade 1994 ("GATT 1994") and Article 4 of the Understanding on Rules and Procedures Governing the Settlement of Disputes ("DSU") regarding the Canada's continued suspension of concessions and other obligations under the covered agreements, after the European Communities' adoption of Directive 2003/74/EC on 22 September 2003 amending Council Directive 96/22/EC concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists. The European Communities has notified this Directive to the DSB and stated that it has fully implemented the recommendations and rulings of the DSB in the dispute *European Communities – Measures Concerning Meat and Meat Products (Hormones)* (*EC – Hormones).* The consultation request was circulated in document WT/DS321/1 dated 10 November 2004. The consultations were held on 16 December 2004 but the parties failed to reach a mutually satisfactory resolution of the dispute.

1.2 On 14 January 2005, the European Communities requested the establishment of a Panel pursuant to Articles 4.7 and 6 of the DSU, as well as Article XXIII of the GATT 1994.[1]

B. ESTABLISHMENT AND COMPOSITION OF THE PANEL

1.3 At its meeting on 17 February 2005, the DSB established a Panel pursuant to the request of the European Communities in document WT/DS321/6, in accordance with Article 6 of the DSU (WT/DSB/M/183), with standard terms of reference as below:

> "To examine, in the light of the relevant provisions of the covered agreements cited by the European Communities in document WT/DS321/6, the matter referred to the DSB by the European Communities in that document, and to make such findings as will assist the DSB in making the recommendations or in giving the rulings provided for in those agreements."[2]

1.4 On 27 May 2005, the European Communities requested the Director-General to determine the composition of the Panel, pursuant to paragraph 7 of Article 8 of the DSU. On 6 June 2005, the Director-General accordingly composed the Panel as follows:

Chairman: Mr. Tae-yul Cho

Members: Mr. William Ehlers
Ms. Claudia Orozco

1.5 Australia, Brazil, China, India, Mexico, New Zealand, Norway, Chinese Taipei and the United States have reserved their rights to participate in the Panel proceedings as a third party.

C. PANEL PROCEEDINGS

1.6 At the joint request of the parties, and on 1 August 2005, the Panel decided that its meetings at which the parties were invited to appear, would be open for observation by the public through closed-circuit broadcast, provided satisfactory logistical arrangements could be maintained by the Secretariat. The Panel, however, after consulting the third parties, also decided that the session with

[1] WT/DS321/6.
[2] WT/DS321/7.

the third parties would remain closed.[3] The Panel notified the DSB Chairman of this decision on the same day.[4] The Panel held its first joint substantive meeting with the parties to this dispute and the parties to the dispute on *United States – Continued Suspension of Obligations in the EC – Hormones Dispute* (WT/DS320) on 12-15 September 2005. The meeting with the parties was open for public observation through closed-circuit broadcast. It also met with the third parties in a closed special session on 14 September 2005.

1.7 The Panel in this dispute also decided to seek advice from scientific and technical experts after consultation with parties on 20 October 2005.[5] After consulting the parties, it finalized its Working Procedures for Consultations with Scientific and/or Technical Experts on 25 November 2005.[6] It selected six scientific and technical experts in consultation with the parties, sought their advice as well as advice from the Codex Alimentarius Commission (Codex), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the International Agency for Research on Cancer (IARC) on scientific and technical questions in writing. The Panel also met with the six experts and four representatives from Codex, JECFA and IARC in the presence of the parties to this dispute and the parties to the dispute on *United States – Continued Suspension of Obligations* (WT/DS320) dispute on 27-28 September 2006. The expert from IARC served both as an individual expert to the Panel and as the representative of the IARC during the meeting. The Panel held its joint second substantive meeting with the parties on 2-3 October 2006. These meetings were also open for public observation through a closed-circuit broadcast.

1.8 On 31 July 2007, the Panel issued its interim report to the parties. On 28 September and 19 October 2007, the Panel received comments from the parties on the interim report. Neither of the parties requested an interim review meeting. On 21 December 2007, the Panel issued its final report to the parties.

II. FACTUAL ASPECTS

A. HISTORY OF THE DISPUTE

2.1 On 13 February 1998, the DSB adopted the Panel and Appellate Body reports in *EC – Hormones*. In doing so, the DSB recommended that the European Communities bring the measures at issue into conformity with WTO rules. The Arbitrator appointed pursuant to Article 21.3(c) of the DSU determined that the European Communities should have a "reasonable period of time" until 13 May 1999 to comply with the recommendations. On 26 July 1999, Canada obtained from the DSB the authorization to suspend obligations up to the level of 11.3 million Canadian Dollars per year. The arbitrators acting pursuant to Article 22.6 of the DSU had previously determined this level to be equivalent to the level of nullification or impairment (Article 22.4 of the DSU) suffered by Canada at the time of its recourse to arbitration in May 1999. On 1 August 1999 and pursuant to the DSB's authorization, Canada introduced import duties in excess of bound rates to imports from the European Communities by imposing a 100% *ad valorem* rate of duty on a list of articles that are the products of certain EC Member States.[7]

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[3] See Annex A-1, Letter to the Parties dated 1 August 2005 on the Panel Decision on Open Hearings for Public Observation. Annex A-2, Working Procedures for the Panel.

[4] WT/DS321/8.

[5] Annex A-3, Letter to the Parties dated 20 October 2005 on the Panel Decision on Consulting Scientific and Technical Experts.

[6] Annex A-4, Letter to the Parties dated 25 November 2005 on the Panel Decision on Certain Issues concerning the Experts' Working Procedures; Annex A-5, Working Procedures for Consultations with Scientific and/or Technical Experts.

[7] The measures were adopted as the "European Union Surtax Order", P.C. 1999-1323, 28 July 1999, published in Canada Gazette Part II, Vol. 133, No. 17, SOR/99-317.

2.2 The original measures in the *EC – Hormones (Canada)* dispute were provided in Directive 96/22/EC, which prohibited the administering to farm animals of substances having a *thyrostatic* action or substances having an *oestrogenic, androgenic*, or *gestagenic* action as well as the placing on market of meat from such animals.[8] On 22 September 2003, the European Communities adopted Directive 2003/74/EC of the European Parliament and of the Council amending Council Directive 96/22/EC concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists. The Directive was published and entered into force on 14 October 2003. It provides for a permanent prohibition on oestradiol-17β and a provisional prohibition on testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate.

2.3 Prior to the adoption of the Directive 2003/74/EC, and in order to comply with the recommendations and rulings of the DSB and the covered agreements, the European Communities initiated and funded a number of specific scientific studies and research projects for the purpose of conducting risk assessment(17 in total). The Scientific Committee on Veterinary Measures relating to Public Health (SCVPH), an independent experts committee established under EC legislation, reviewed the results of these studies and other publicly available information as well as the data it collected from various sources including CODEX/JECFA, and published its opinion entitled "Assessment of Potential Risks to Human Health from Hormones Residues in Bovine meat and Meat Products" ("the 1999 SCVPH Opinion") on 30 April 1999. The SCVPH subsequently reviewed this Opinion on two occasions and adopted review reports on 3 May 2000 (" the 2000 SCVPH Opinion") and on 10 April 2002 (the 2002 SCVPH Opinion"). The SCVPH Opinions address six hormonal substances: *oestradiol-17β, testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate*.[9]

2.4 In light of these Opinions, which the European Communities contends are risk assessments, the European Communities prohibited the placing on the market of meat and meat products from animals that have been treated with oestradiol-17β for growth promotion purposes on the grounds that there was a substantial body of evidence showing that its residues are both carcinogenic and genotoxic. With respect to testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate, the European Communities introduced the same measure on a provisional basis on the grounds that the available pertinent scientific information reflected in the above-mentioned SCVPH Opinions showed the existence of risks, but all the information and data necessary to conduct a more objective and complete risk assessment were insufficient or missing.[10]

2.5 On 27 October 2003, the European Communities notified to the DSB the adoption, publication and entry into force of the Directive. In the same communication, the European Communities explained that it considers itself to have fully implemented the recommendations and rulings of the DSB in the *EC – Hormones* dispute and as a consequence, it considers the Canada's suspension of concessions vis-à-vis the European Communities to be no longer justified.[11]

2.6 Canada disagreed in the DSB meeting held on 7 November 2003 that the new Directive was based on science and stated that it would not remove the retaliatory measures vis-à-vis the European Communities.[12]

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[8] WT/DS48/R/CAN, paras. 2.1-2.5.

[9] See, Request for the Establishment of a Panel by the European Communities, WT/DS321/6.

[10] Ibid. S*ee also* the EC's second written submission, para. 134.

[11] *European Communities – Measures Concerning Meat and Meat Products (Hormones)*, Communication from the European Communities, WT/DS26/22, WT/DS48/20, 28 October 2003.

[12] DSB, Minutes of Meeting held on 7 November 2003, WT/DSB/M/157, 18 December 2003, para.31; See also the Request for the Establishment of a Panel by the European Communities, WT/DS321/6.

B. MEASURE AT ISSUE

2.7 The measure challenged by the European Communities is the suspension of concessions and other obligations under the covered agreements, continued without recourse to the procedures under the DSU, after the European Communities' adoption of Directive 2003/74/EC on 22 September 2003 amending Council Directive 96/22/EC concerning the prohibition on the use in stock-farming of certain substances having a hormonal or thyrostatic action and of beta-agonists. The measure is provided in Canada's *European Union Surtax Order* and is enforced as of 1 August 1999. The EC's Directive was published and entered into force on 14 October 2003. The EC stated in its notification to the Dispute Settlement Body (DSB) that it has fully implemented the recommendations and rulings of the DSB in the dispute *European Communities – Measures Concerning Meat and Meat Products (Hormones)* (WT/DS48/AB/R ,WT/DS48/R/CAN).[13]

III. PARTIES' REQUESTS FOR FINDINGS AND RECOMMENDATIONS

3.1 The European Communities requests the Panel to find that Canada's unilateral conduct:

(a) violates Article 23 of the DSU and, more specifically, Article 23.2(a), read in conjunction with Article 21.5 and Article 23.1 of the DSU;

(b) violates Article 23.1 of the DSU read in conjunction with Articles 22.8 and 3.7 of the DSU; and

(c) violates Articles I and II of the GATT 1994.[14]

3.2 In the alternative, should the Panel find no violation of Article 23 of the DSU, the European Communities requests the Panel to find that Canada's measure violates Article 22.8 of the DSU and Articles I and II of the GATT 1994.[15]

3.3 Canada requests the Panel to reject the European Communities' claims and find that Canada has not maintained its suspension of concessions with regard to the European Communities in contravention of Articles 3.7, 21.5, 23.1, 23.2(a) and 22.8 of the DSU, and Articles I and II of the GATT 1994.[16]

IV. ARGUMENTS OF THE PARTIES

A. INTRODUCTION

4.1 The arguments of the parties are set out in their written submissions to the Panel and in their oral statements made during Panel meetings, as well as in their written replies to questions from the Panel. This Section presents a summary of the arguments of parties based on the executive summaries prepared by the parties where such summaries were made available to the Panel.

B. PARTIES' REQUESTS AND ARGUMENTS ON OPENING THE PANEL MEETING FOR THE PUBLIC OBSERVATION

4.2 At the Panel's organizational meeting with the parties on 13 June 2005, the parties requested that the Panel hold open meetings with the parties in this dispute. The Panel posed written questions

[13] WT/DS321/6, WT/DS26/22, WT/DS48/20.
[14] EC's first written submission, para. 150.
[15] EC's first written submission, paras. 24 and 151.
[16] Canada's first written submission, para. 133.

to the parties and the third parties regarding this joint request after its organizational meeting. The parties answered these questions in writing on 20 June 2005 and on 7 July 2005.

1. Arguments of the European Communities

(a) Whether panels are permitted to open hearings under Article 12 (including Appendix 3), Articles 14.1 and 17.10 of the DSU

4.3 The European Communities argues that open hearings are permissible at the panel level. The European Communities submits that Appendix 3, second paragraph, first sentence of the DSU excludes public access to panel hearings, but this rule is not obligatory, as Article 12.1 of the DSU states: "Panels shall follow the Working Procedures in Appendix 3 unless the panel decides otherwise after consulting the parties to the dispute." In the European Communities' view, it is therefore permissible for a panel to adopt, under the procedure of Article 12.1 of the DSU, working procedures that foresee open hearings.

4.4 The European Communities also argues that this conclusion is not affected by Article 14.1 of the DSU. The term "deliberations" under Article 14.1 of the DSU designates the part of the panel's work where it internally discusses the case, including the decision it intends to pronounce in its report and the supporting reasoning. This is the ordinary meaning of this term, in which it is also used in other systems of adjudication, and the French ("délibérations") and Spanish versions ("deliberaciones") fully coincide with this meaning. These deliberations take place in the presence of the Secretariat team working on the dispute, but without the parties. The term "deliberations" does not cover the meetings with the parties, for which different terminology is used in Appendix 3 of the DSU. The context supports this reading because everything that is addressed in the three paragraphs of Article 14 of the DSU relates to the independent work which the panel conducts alone, in the absence of the parties. Had the drafters of the DSU wanted to exclude open panel hearings, they would have used a different language in Article 14.1 of the DSU. They would not have addressed this question solely in the Appendix 3 working procedures from which a panel may depart, as Article 12.1 expressly stipulates.

4.5 In the European Communities' view, this interpretation is also corroborated by the use of the term "proceedings" in Article 17.10 of the DSU which appears to be broader. Meaning must therefore be given to the DSU negotiators' deliberate choice of the term "deliberations" in Article 14.1 of the DSU.

4.6 The European Communities argues that such interpretation is the long-standing position of several Members and has never been rejected by any WTO Member in any dispute. WTO Members have repeatedly stated that the DSU rules on panel procedures are flexible and allow the provision of open hearings (Articles 14.1, 12.1, Appendix 3). Obviously, since a panel is obliged to consult the parties before departing from the working procedures suggested in Appendix 3, the parties' position carries significant weight for the panel's decision. The EC considers that in the present case where all the parties have agreed to open hearings, the Panel should accommodate the parties' request. Article 18.2 of the DSU also provides context and supports this position as it implies that parties are entitled to "waive" the confidentiality of their positions.

(b) Legal implications of open hearings on covered persons under the Rules of Conduct

4.7 The European Communities considers that no legal issues arise under the Rules of Conduct. These Rules state in Section II, paragraph 1 that each covered person "shall respect the confidentiality of proceedings" (see also Section VII, paragraph 1), and also that "[t]hese Rules shall in no way modify the rights and obligations of Members under the DSU nor the rules and procedures therein." In the European Communities view, the Rules of Conduct are and remain fully binding on all covered

persons in this dispute, even if the hearings are opened to the public. Simultaneously, the Rules of Conduct do not prevent the panel from fulfilling its task under the DSU and in accordance with the procedural rules contained therein, which permit public hearings. The Rules of Conduct expressly state that they do not modify these DSU rules.

4.8 The European Communities also considers that Article 18.2 of the DSU again provides context in that it shows that parties are entitled to "waive" the confidentiality of their positions. The Panel's deliberations will in any event not be affected by the opening and remain confidential, as required by Article 14.1 of the DSU.

(c) Systemic and political impact of opening hearings

4.9 The European Communities is of the view that there are no implications for WTO Members who are not parties to this dispute, notably the parties to another dispute remain able to adhere to their preference, if any, not to open the hearings in their dispute. Opening a hearing for observers who will remain completely passive during the session would not change anything about the intergovernmental character of the WTO, nor would it impair the chances to reach a mutually agreed solution, as preferred by the DSU (Article 3.7), if the parties jointly request the hearings to be open, in line with their general policy to apply transparency where the DSU rules allow (for instance by making public their submissions). Also, there are no implications for third parties and accordingly there is no need to consult them before the Panel adopts its working procedures because the parties have jointly requested that the public be excluded from the third parties' session during the presentation by a third party who prefers this. Thus, opening hearings to public observation will not affect third parties beyond the extent to which they themselves agree. The DSU is clear in that the panel must consult the parties, not the third parties, before adopting Working Procedures in departing from Appendix 3.

4.10 The European Communities also states that consulting the DSB and General Council Chairs or the Director-General before opening the hearing for public observation does not seem necessary because under the DSU the Panel has the power to take decisions regarding its Working Procedures and is required to fulfil its task in full independence. If all parties are in agreement on this question of working procedures, the Panel should accommodate their request if the parties consider that this is part of the best way to "secure a positive solution to the dispute", which is the aim of the dispute settlement mechanism (Article 3.7 of the DSU).

(d) What procedures can be adopted to protect confidential information in an open hearing

4.11 The European Communities indicates that it does not expect that confidential information will be submitted in this dispute. Should this nevertheless happen, one could easily apply appropriate means to close the portion of any meeting where confidential information is discussed.

4.12 The European Communities does not consider that there is any issue of confidentiality in relation to information submitted by other Members or non-Members (under Article 13 of the DSU), unless the confidentiality requirement of the last sentence of Article 13.1 of the DSU applies, in which case the corresponding portion of any meeting where this information is discussed could be closed.

4.13 With respect to the third party session, the European Communities considers that each third party should decide whether to open the part of the third party session dealing with that third party's statement.

2. Arguments of Canada

(a) Whether panels are permitted to open hearings under Article 12 (including Appendix 3), Articles 14.1 and 17.10 of the DSU

4.14 Canada argues that the DSU allows for open hearings of WTO panels. Article 14.1 of the DSU states that panel "deliberations" shall be confidential. The reference to "deliberations" indicates that this paragraph applies to the internal deliberations of panels, not to the panels' meetings with the parties. Furthermore, paragraph 2 of the Working Procedures in Appendix 3 of the DSU, which refers to closed panel meetings, is subject to DSU Article 12.1, which specifically allows a panel to deviate from the Working Procedures in Appendix 3 after consulting parties to the dispute. In cases such as this one, where all parties to the dispute have agreed to open hearings, Canada is of the view that the Panel should accommodate such a request. This position is consistent with the right of all parties to waive confidentiality as expressed in Article 18.2 of the DSU, which states that a party is not precluded from disclosing statements of its own positions to the public. In the present case, it is clear that all parties have agreed beforehand to waive their right to confidentiality during the panel hearings.

(b) Legal implications of open hearings on covered persons under the Rules of Conduct

4.15 Canada argues that the relevant provision in the Rules of Conduct is paragraph VII.1, which provides: "[e]ach covered person shall at all times maintain the confidentiality of dispute settlement deliberations and proceedings together with any information identified by a party as confidential. No covered person shall at any time use any information acquired during such deliberations and proceedings to gain personal advantage or advantage for others. "

4.16 This provision, in Canada's view, requires confidentiality on the part of members of a panel of deliberations and proceedings. However, in accordance with paragraph II:1 of the Rules of Conduct, which expressly states that these Rules do not modify the rules and procedures under the DSU, this provision is subject to a decision of the Panel to hold public hearings pursuant to Article 12.1 of the DSU. Therefore, Canada considers that the obligation of covered persons to maintain the confidentiality of a panel proceedings continues to apply but is modified to the extent that the Panel has decided to hold public hearings.

(c) Systemic and political impact of opening hearings

4.17 Canada considers that opening the panel meetings to the public can only contribute to the legitimacy, and perception of legitimacy, of the dispute settlement process. The desire of the disputing parties to hold open hearings in this case does not have any broader systemic or political implications – it merely serves the interests of the disputing parties in this case consistent with the institutional framework of the WTO and with Article 12.1 of the DSU.

4.18 Canada submits that Article 12.1 of the DSU requires that panels decisions on their working procedures be taken in view of consultation with parties. This provision does not require consultation with third parties. However, Canada recognizes that third parties may have requested third party status with the expectation of participating in closed proceedings. Therefore, Canada suggests that after the Panel decides to hold public hearings it should consult with third parties to (a) identify any concerns of third parties regarding their participation in the proceedings, and (b) explore possible steps to accommodate such concerns. Such accommodation measures may include turning off cameras during the delivery of oral statements of third parties that do not wish to deliver such an oral statement in a public hearing. Canada does not see a need for the Panel to consult with the Chairs of the DSB, of the General Council or of the DSB Special Sessions, or with the Director General.

(d) What procedures can be adopted to protect confidential information in an open hearing

4.19 Canada believe that a provision should be added to the Working Procedures that would provide a mechanism to protect business-confidential information that may become the subject of discussion during the public hearings. Canada recommends a procedure under which a party may request the Panel to suspend the public nature of the hearing for as long as such business-confidential information was being discussed.

4.20 As to the third parties, Canada submits that they will have to follow the provisions in the Working Procedures adopted by the Panel pursuant to DSU Article 12. Thus it is open to the Panel to decide that the oral statements by third parties will take place in public meeting. However, it is also within the Panel's discretion to leave it to the choice of individual third parties whether they wish to make their oral statements in a private or public session. Canada prefers giving third parties such a choice. Canada recommends the adoption of a practical procedural mechanism to suspend the public nature of the hearing as necessary.

4.21 The treatment of written materials presented by other WTO Members or by non-Members falls outside the scope of issues raised by the possible public nature of the hearing. None of the parties has proposed a modification to the Working Procedures that would expand the categories of participants in the hearing. Nevertheless, Canada recognizes that the written evidence provided by other WTO Members or non-Members may have been provided in confidence. To the extent that such confidential information is discussed during the hearings, there will be need to add to the Working Procedures a provision that would permit the Panel to interrupt the public nature of the hearing before a discussion of such confidential written materials takes place. In Canada's view, such a procedure should be similar to that outlined above in respect of business-confidential information.

C. FIRST WRITTEN SUBMISSION OF THE EUROPEAN COMMUNITIES

1. Introduction

4.22 This case is about procedural obligations under the DSU of Members that continue to apply the suspension of concessions or other obligations after almost two years despite the proper notification by the responding party that it has adopted the necessary measures to implement the DSB recommendations and rulings. In the alternative, the European Communities makes conditional substantive claims under Article 22.8 of the DSU and Articles I:1 and II of the GATT 1994.

2. Factual aspects

4.23 Following an authorization by the DSB, Canada suspended tariff concessions and other related obligations up to the level of Canadian $ 11.3 million. Subsequently, the European Communities implemented the original DSB recommendations and rulings by Council Directive 2003/74/EC. However, Canada continues to suspend concessions and related obligations against certain products originating in the European Communities based on a unilateral determination that the EC's implementation measure is insufficient to comply with the DSB recommendations and rulings.

3. Legal arguments: Part I – Violation of Articles 23, 21.5, 22.8 and 3.7 of the DSU and Articles I and II of the GATT 1994

(a) The structure of Article 23 of the DSU

4.24 Article 23 of the DSU lays down the fundamental principle that the dispute settlement system of the WTO is the exclusive means to redress any violation of any provision of the WTO Agreement.

Any attempt to seek "redress" can take place only in the institutional framework of the WTO and pursuant to the rules and procedures of the DSU. This has been confirmed in *US – Section 301 Trade Act* and *US – Certain EC Products.*

4.25 Article 23.1 of the DSU contains a general obligation to follow the rules and procedures of the DSU whereas Article 23.2 of the DSU lists a number of "specific and clearly-defined forms of prohibited unilateral action." The relationship between the two paragraphs has two distinguishing features. First, Article 23.2 of the DSU has to be read in the context of the first Paragraph ("in such cases"), that is, it has to be established that the Member's action is performed with a view to redressing a WTO violation. Second, the specific forms described in Paragraph 2 do not exhaust the list of prohibited unilateral action. There is a relationship of *lex specialis* and *lex generalis* which implies, on the one hand, that whenever there is a violation of a specific case in Paragraph 2 of Article 23, there always is also a violation of Paragraph 1 of that provision; and on the other hand, that a particular conduct that may not come under the specific cases listed in paragraph 2 of Article 23, may still constitute a violation under paragraph 1 of that provision.

(b) Applicability of Article 23 – Article 23.1 of the DSU: Seeking the redress of a WTO Violation

4.26 The meaning of "seeking the redress of a violation" under Article 23.1 of the DSU has been extensively discussed by previous panels, i.e. *US – Section 301 Trade Act* and *US – Certain EC Products*. The "violation" with regard to which redress is sought need not be one that has been identified as such by the relevant WTO bodies. It suffices if it is perceived as being one by the Member in question. The suspension of concessions or other obligations is a means of "redress." Indeed it is the very means the WTO system envisages as a last resort remedy to WTO violations according to Articles 3.7 and 22.1 of the DSU.

4.27 It is obvious that when it suspended concessions in August 1999, Canada was seeking to redress a (WTO-determined) violation. Back then, Canada reacted to the European Communities' failure to implement, within the reasonable period of time, the DSB recommendations in the *EC – Hormones* case. It requested and obtained a DSB authorization under Article 22.2 (respectively 22.7) of the DSU, following which Canada decided on the imposition of 100% additional duties. Canada's way of proceeding back then is the very example of "seeking to redress a WTO violation" in line with the rules and procedures of the DSU.

4.28 There can equally be no doubt that, if Canada is continuing the suspension of concessions to this day despite the European Communities' adoption of an implementation measure, it does so because it still is seeking to redress a WTO violation. This can already be deduced from the fact that the August 1999 measure of applying duties in excess of bound rates is being continued without there being any modification to it. Since that measure is motivated to be imposed as "a result of the EC's failure to implement the recommendations and rulings of the WTO," and since Canada has neither abolished nor changed the measure, nor modified its reason, Canada is obviously of the view that the EC's failure to implement the recommendations and rulings of the WTO still persists. Indeed, the continuation of the suspension of concessions is an unequivocal indication that Canada believes that there continues to be a violation. Otherwise it would have ended the suspension of concessions in accordance with its obligations under Article 22.8 of the DSU. Moreover, this is the explicit view Canada has formally taken in the DSB and in various official statements.

(c) Violation of Articles 23.2(a) and 21.5 and of Article 23.1 of the DSU

4.29 Canada's conduct is contrary to the specific prohibition of unilateral conduct set out in Article 23.2(a) of the DSU. Instead of seeking redress of the perceived continued failure of the European Communities to implement the DSB's recommendations and rulings through the continued

suspension of concessions, Canada should have introduced a compliance procedure under Article 21.5 of the DSU. Because it has not done so, it has violated the specific prohibition of unilateral conduct set out in Article 23.2(a) of the DSU. This violation of Article 23.2(a) and 21.5 constitutes at the same time a violation of Article 23.1 of the DSU.

4.30 As the Panel in *US – Section 301 Trade Act* has noted, the following conditions need to be fulfilled in order to find a violation of Article 23.2(a) of the DSU. First, given the "chapeau" of Article 23.2, it needs to be established that there is "such a case", namely that a Member is seeking to redress a WTO violation. This is the case here.

4.31 Second, Article 23.2(a) of the DSU requires that a Member has made a "determination to the effect that a WTO violation has occurred." The ordinary meaning of the term "determination," has been noted by the Panels in *US – Section 301 Trade Act* and *US – Certain EC Products.* Such a decision need not have a specific form, and can be inferred from action. The suspension of concessions or other obligations is the very means (albeit of last resort) to react to a violation and therefore necessarily implies a decision that there is a violation. That such a decision bears consequences in WTO trade relations hardly requires any explanation. The present case is similar to the situation in *US – Certain EC Products.* Again, the action in question is the suspension of concessions and related obligations. In contrast to the above case, nevertheless, the suspension here had initially been authorized by the DSB based on a multilateral determination that there was a violation. This multilateral determination, however, was made with respect to the measures applied by the European Communities at the time. Logically, it could not and did not apply to the measures subsequently adopted and properly notified to the WTO by the European Communities. With regard to the current legislative situation in the European Communities, no multilateral determination has been made by the time at which this Panel was established. If Canada nevertheless continues to apply the suspension of concessions and related obligations, it necessarily implies that it has unilaterally determined that there continues to be a violation. It has, in addition, explicitly said so.

4.32 Third, Article 23.2(a) of the DSU is violated if the determination is not made in accordance with the rules and procedures of the DSU, or is not consistent with the findings of a dispute settlement organ. The DSU provides for a specific procedure, namely Article 21.5 of the DSU, to address the situation that Members disagree over the existence or consistency of measures taken to comply with the recommendations and rulings of the DSB.

4.33 There exists obviously a disagreement as to whether or not, by adopting Directive 2003/74/EC, the European Communities has implemented the recommendations and rulings from the DSB in the *EC – Hormones* case. Article 21.5 of the DSU requires that disagreement *shall* be decided through recourse to dispute settlement. The European Communities has invited several times Canada, but, to date, it refuses to initiate a compliance procedure under Article 21.5 (or, for that matter, any other dispute settlement procedure under the DSU). Instead, it simply continues to apply the suspension of concessions and related obligations as if no "measure to comply" had been taken or the non-compliance of the new directive of the European Communities had already been established.

4.34 As the determination in the present case has been made *before* the commencement, let alone the exhaustion of the Article 21.5 procedure, it is necessarily not one that has been made consistent with the findings contained in an adopted panel or Appellate Body report.

(d) Canada's continued suspension of concessions and related obligations is in violation of Article 23.1, read together with Articles 22.8 and 3.7 of the DSU

4.35 Under Article 23.1 of the DSU, Canada is obliged to have recourse to, and abide by, the rules and procedures of this Understanding. This encompasses, *inter alia*, Articles 22.8 and 3.7 of the DSU. In this respect, the following should be noted.

4.36 The suspension of concessions or other obligations is limited in time. This temporal limitation is the very foundation of the retaliation system under the DSU. The importance of this principle is already demonstrated by the fact that the "temporary nature" of countermeasures appears contextually at two places in Article 22 of the DSU, in Paragraph 8 and in Paragraph 1. The temporal limitation is a practical consequence of the fact that suspension of concessions should only be applied as "a last resort", Article 3.7 of the DSU. This means that the suspension of concessions should only apply where justified and necessary.

4.37 The temporary nature of the suspension of concessions or other obligations has been recurrently interpreted by arbitrators to indicate that one of the main objects and purposes of sanctions is to induce compliance by the violating WTO member with its obligations. Indeed, in reaching this conclusion the arbitrators followed a suggestion by Canada (see *EC – Bananas III (US) (Article 22.6 – EC)*). The objective of inducing compliance entails, however, that once a Member has adopted compliance measures which are not properly challenged by the complaining Member, the suspension of concessions or other obligations can not be applied any longer. Indeed, in such a scenario the suspension of concessions or other obligations would be deprived of one of its main objectives, i.e. to achieve implementation of a DSB decision, for the simple reason that the WTO Member has already taken measures to implement the DSB recommendation. In this case, the objective to induce compliance can only revive after it has been properly established that the implementing measure has been insufficient to remedy a WTO violation.

4.38 Article 22.8 of the DSU prohibits the continued unilateral application of the suspension of concessions or other obligations when the measure which has been found inconsistent is removed. The term "removed" thereby refers to the compliance by a WTO Member because this provision is based on the respect of the WTO obligations by the Member concerned (see Article XVI:4 of the WTO Agreement and Article 19.1 of the DSU). The scope of the compliance obligation is determined by the DSB recommendations and rulings following the adoption of the Panel and/or Appellate Body report (Articles 21.5, 22.2 of the DSU).

4.39 Article 22.8 of the DSU does not specify how the removal of the WTO inconsistency is determined. However, in the light of its context, i.e. Articles 21.5 and 23.2(a) of the DSU, and given the exceptional nature of countermeasures, i.e. their temporal limitation, it is clear that a Member can not unilaterally determine that the WTO inconsistency persists despite the notification of a compliance measure. In very much the same vein, a Member can not decide to continue to suspend concessions or other obligations unilaterally. The WTO inconsistency of the implementing measure can only be determined in accordance with the appropriate procedure, namely Article 21.5 of the DSU. Unless such a procedure concludes that the compliance measure does not fully implement the DSB recommendations and rulings, it cannot be presumed that this is the case.

4.40 This also follows from the general principle of good faith as it applies in international State relations, under which States are normally considered to act in conformity with their obligations. This principle has been widely confirmed in the international (trade) jurisprudence (see ICJ *Corfu Channel*, *EC – Hormones (Article 22.6)*, *Chile – Alcoholic Beverages*, *Canada – Aircraft (Article 21.5 – Brazil)* and it also applies for implementing measures (*Canada – Dairy (Article 21.5 – New Zealand and US II)*, *EC – Bed Linen (Article 21.5 –India))*.

4.41 Therefore, it is clear that Canada could not unilaterally determine that the European Communities implemented the DSB recommendations and rulings in a WTO inconsistent way. To the contrary, the European Communities must be presumed to have complied with its WTO obligations, if Canada refuses to establish the contrary.

4.42 Once the inconsistency of the measure has been removed, Article 22.8 of the DSU provides that "the suspension of concessions or other obligations shall be temporary and shall only be applied

until such time as the measure found to be inconsistent with a covered agreement has been removed." This provision is mandatory. It does not leave any margin of discretion to the retaliating Member, thereby corroborating the exceptional nature of the imposition of countermeasures. As explained above, a Member which contests the removal of the inconsistency of the measure has to abide by the rules and procedures under the DSU, i.e. Article 21.5 of the DSU. Only if it is established in such a procedure that the WTO inconsistency persists is the application of the suspension of concessions or other obligations permissible under Article 22.8 of the DSU.

4.43 Under the same logic, Article 22.8 of the DSU does not allow for the application of countermeasures on the basis of a *unilateral* determination regarding the WTO inconsistency of the measure. Rather, Article 22.8 of the DSU, read in its context with Articles 21.5 and 23.2(a) of the DSU, requires that in the absence of an adverse finding, the suspension of concessions or other obligations shall not "be applied" any longer. This language is open in, at least, three directions:

4.44 Firstly, it indicates that the suspension of concessions or other obligations must be terminated in case a compliance measure is not challenged, the measure thus being accepted as being in full accordance with the WTO agreements.

4.45 Secondly, Article 22.8 of the DSU shows that the suspension of concessions or other obligations must not be applied any longer if the complaining Member delays, postpones or refuses the initiation of an Article 21.5 proceeding. As a WTO Member is presumed to act in conformity with its obligations, it follows necessarily that through the compliance measure it is presumed to have removed the WTO inconsistency of the measure at least when the following three conditions are fulfilled: (1) the Member has followed its internal decision-making procedures that are normally applied for the purpose of adopting compliance measures of that kind; (2) the elaboration, deliberation and adoption of the compliance measure is done in an open and transparent manner, and (3) the compliance measure is notified properly to the WTO. Therefore, the suspension of concessions or other obligations should not apply any longer. This case is particularly relevant in the present dispute where Canada has been refusing for almost two years to initiate the compliance procedure under Article 21.5 and to cease the suspension of concessions and related obligations against the European Communities. Thus, Canada continues the suspension of concessions and related obligations on the basis of a unilateral determination regarding the WTO-inconsistency of the notified compliance measure.

4.46 In the light of the two first conclusions, it would also be appropriate to infer from Article 22.8 read together with Article 23.1 of the DSU that the suspension of concessions or other obligations should not continue to be applied until the WTO inconsistency of the properly notified measure has been positively determined by the DSB.

4.47 This result is also corroborated by the system and overall thrust of Article 23 of the DSU, which is to strengthen the multilateral system. If a WTO Member were allowed to continue the application of suspension of concessions without challenging the implementing measure, it would necessarily have to base its assessment on a unilateral determination of the WTO inconsistency of the new measure. This would be in plain contradiction to Article 23.2(a), in conjunction with Article 21.5 of the DSU, as explained above.

4.48 The scenario described above follows the same *ratio legis* that applies for the initial imposition of suspension of concessions or other obligations. Thus, whether a Member suspends for the first time concessions or other obligations or wishes to maintain the suspension despite an implementation act does not make a difference. In both cases, a Member must not substitute unilaterally its assessment of a WTO inconsistency of an implementation measure to the procedures under the DSU.

4.49 In the case of the initial imposition of suspension of concessions or other obligations, the DSU implies first a determination that the Member concerned has not implemented the DSB recommendations and rulings. The DSB would not authorize the suspension of concessions or other obligations, if a WTO Member has taken implementing measures. It is established practice that the Member which intends to suspend concessions or other obligations first obtains a DSB decision regarding the insufficiency of the implementing measure following an Article 21.5 of the DSU proceeding. This normal course of events and legal steps in the case of the imposition of suspension of concessions or other obligations is in full accordance with the overarching principle set out in Article 23 of the DSU prohibiting Members from making unilateral determinations that another Member has violated its obligations.

4.50 Regarding the question of the conditions under which the suspension of concessions or other obligations could be *maintained*, there is no reason to assume that this fundamental logic should change in any way whatsoever. In fact, the legal situation is identical where the implementing Member has taken the necessary measures to comply with its WTO obligations in accordance with its internal rules and procedures and notified the measures in question to the WTO.

4.51 This comparability is even more striking if one focuses on the timing of an implementation measure. In the case of the initial *imposition* of the suspension of concessions or other obligations, a WTO Member has not implemented its obligations *before* the DSB's authorization to suspend concessions or other obligations. In the case of the *maintenance* of suspension of concessions or other obligations, a WTO Member implements its obligations *after* the DSB's authorization to suspend concessions or other obligations. This difference in timing, however, does not alter the normal legal sequencing between the multilateral review of the compliance measure and the application of suspension of concessions or other obligations. Indeed, the sole difference in timing does not give the retaliating Member all of a sudden the substantive right to make *unilateral* decisions as to whether or not the implementing measure is appropriate and sufficient and, if it is not considered sufficient, to continue applying the countermeasures as if nothing had happened.

4.52 In light of the above, there is an absolute need to refrain from continuing to apply the suspension of concessions or other obligations in cases where the retaliating Member has not properly challenged the compliance measure in an Article 21.5 proceeding. In fact, if a Member were allowed to maintain the suspension of concessions or other obligations even in such a new legal situation, it could make the kind of unilateral determinations which Article 23 specifically outlaws. Also, it could continue to apply the suspension of concessions or other obligations even if the WTO violation has been objectively removed. The implementing Member would then have to suffer from the suspension of concessions or other obligations even though it has fully abided by its obligations. It goes without saying that such a result would be in plain contradiction to the DSU provisions governing the suspension of concessions or other obligations, in particular Articles 3.7 and 22.

4.53 These fundamental principles are not altered by the fact that there exists a DSB authorization under Article 22.7 of the DSU to suspend concessions or other obligations. The DSB authorization cannot change the fundamental rules under the DSU. Rather, the DSB implements these rules. Thus, as the DSU provides that the suspension of concessions or other obligations should not be applied unless a WTO violation by a Member's measure has been properly established, the DSB authorization cannot be interpreted to justify such a suspension if a WTO violation of a Member's (new) measures has not been properly determined.

4.54 The basis for a DSB authorization to suspend concessions or other obligations is a prior *multilateral* determination that the implementing WTO Member has failed to comply with its obligations. This is the case if an Article 21.5 proceeding concludes that the implementing measure was insufficient. This is also implicitly the case if a Member has not adopted any implementing measure at all at the time of the DSB decision under Article 22.7 of the DSU. On the contrary, if a

WTO Member implements properly its obligations after the DSB has authorized the suspension of concessions or other obligations the basis for this decision changes fundamentally. As the original DSB authorization was taken in view of the original measure, it cannot logically encompass the new implementing measure. Hence, the DSB authorization cannot cover the continued application of the suspension of concessions or other obligations, if a WTO Member subsequently implements its obligations in the absence of a multilateral review regarding the compliance (or not) of this new measure.

4.55 Regarding this DSB authorization it is once again useful to compare the two situations of the *imposition* and the *maintenance* of the suspension of concessions or other obligations. The DSB could not authorize the imposition of retaliatory measures under Article 22.7 of the DSU, if the implementing Member had undertaken measures to comply with its obligations and if those had not been found WTO inconsistent following an Article 21.5 proceeding. In the very same vein, the DSB authorization cannot justify the maintenance of suspension of concessions or other obligations if a Member properly complies with its obligations after the imposition of these measures and if its compliance measure is not challenged in an Article 21.5 proceeding. Again, the mere temporal difference of the new implementing measure does not mean that the DSB authorization, once received, serves as a blank authorization for a Member to continue the application of the suspension of concessions or other obligations indefinitely in the future and on the basis of unilateral determinations.

4.56 Furthermore, the European Communities would note that, from a systemic point of view, Article 22.8 of the DSU is subsequent to Article 22.7 of the DSU. This indicates that once the situation under Paragraph 8 occurs it overtakes the authorization granted under Paragraph 7. Paragraph 8 conditions Paragraph 7. As it must be assumed that the DSU negotiators followed a logical sequencing in the way they drafted Article 22, it is clear that Article 22.8 of the DSU was supposed to impact on the authorization under Article 22.7 of the DSU. Indeed, to assume that the removal of the inconsistency of the measure under Paragraph 8 has no impact on the DSB authorization under Paragraph 7 is not legally coherent or reasonable.

4.57 Moreover, this reading of the DSB authorization is corroborated if one takes a closer look at the substance of this authorization. The level of nullification or impairment has to be determined in relation to the violation determined for the existing measure (Article 3.8 of the DSU). Thus, assuming that a WTO Member has not undertaken any implementation steps, the level of nullification should be determined in relation to the original violation. But assuming, in a second scenario, that a Member has implemented partly or fully its WTO obligations, the level of nullification or impairment would have to be determined accordingly. Obviously, in the area where the Member implemented properly its obligations there would be no nullification or impairment. This logic had also been recognized by the arbitrators in *EC – Bananas III (US) (Article 22.6 – EC).*

4.58 Applying the same reasoning in the present case, it is clear that the level of suspension of concessions or other obligations as authorized by the DSB was based on a non-implementation by the European Communities. However, this level and, therefore, the scope of the authorization may not be justified any longer once the European Communities has properly implemented its obligations.

4.59 Finally, following the jurisprudence by the Appellate Body, once a Member violates Article 23.1 read in conjunction with Article 22.8 of the DSU, it necessarily also acts contrary to Article 3.7 of the DSU.

(e) Canada is in violation of Article I:1 of the GATT1994 because of the continued suspension of concessions and related obligations

4.60 Canada is acting inconsistently with Article I:1 of the GATT 1994 by imposing import duties in excess of bound rates on products originating in certain EC Member States.

(f) Canada is acting inconsistently with Article II of the GATT 1994 by the continued application of countermeasures on products originating in the European Communities.

4.61 Canada is violating its obligations under Article II:1(a) and Article II:1(b) of the GATT by suspending concessions and related obligations against the European Communities.

4. Legal arguments: Part II – Conditional claim in the event that the Panel does not find any violation of Article 23 of the DSU as set out in Part I

(a) Canada is violating Article 22.8 of the DSU because the measure found to be inconsistent has been removed by the European Communities

4.62 Canada is violating Article 22.8 of the DSU by continuing to suspend concessions and related obligations even though the measure found to be inconsistent has been removed. Consequently, Canada is under an obligation not to apply the suspension of concessions any longer. In the following, the European Communities will set out in more detail why the new measure is not only in presumed compliance as argued above but in actual compliance with the recommendations and rulings of the DSB.

4.63 The rulings of both the Panel and the Appellate Body had essentially turned on the reading of Article 5.1 of the *SPS Agreement*, and in particular, the requirement that a measure be based on a risk assessment. The Appellate Body upheld the Panel's finding that the EC measures at issue were inconsistent with the requirements of Article 5.1 of the *SPS Agreement*. At the same time, the report contains an important clarification as to how the European Communities could bring its regime for hormones-treated meat in accordance with its obligations under the covered agreements. As seen above in relation to Part I, the Appellate Body held "that Article 5.1, read in conjunction with Article 2.2, requires that the results of the risk assessment must sufficiently warrant the SPS measure at stake."

4.64 On the basis of the scientific data presented by the European Communities, the Appellate Body found that that data did not sufficiently warrant or reasonably support the import prohibition. The Appellate Body found, in particular, that the scientific reports and studies submitted by the European Communities did not rationally support the EC import prohibition or were too general, i.e. relevant but not sufficiently specific to the case. It is important to understand, therefore, that the Appellate Body did not find that an import prohibition for beef from hormone treated cattle was *per se* in violation of the *SPS Agreement.* Rather it found that the EC import prohibition was not sufficiently warranted, that is to say reasonably supported, by the specific risk assessment relied upon at that time by the European Communities.

4.65 In order to comply with the above findings the European Communities conducted a comprehensive risk assessment. The risk assessment focussed on potential risks to human health from hormone residues in bovine meat and meat products, in particular such risks arising from residues of the six hormonal substances (oestradiol-17β, testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate). In carrying out the risk assessment, the European Communities initiated and during 1998-1999 funded altogether 17 specific scientific studies and research projects in order to obtain as much as possible of the missing scientific information as identified in the above rulings. Moreover, the European Communities addressed in 1998 specific requests for the submission of

scientific data to the United States, Canada, Australia and New Zealand which all authorize the use of these six hormones for animal growth promotion. It also published an open call for documentation requesting any interested party, including the industry, to provide any relevant and recent scientific data and information in their possession to be taken into account in the complementary risk assessment.

4.66 The data collected was submitted to the *Scientific Committee on Veterinary Measures relating to Public Health* (SCVPH), an independent expert Committee established under EC legislation to evaluate this kind of substances on the EC legal system. This scientific body was the one responsible for scientific and technical questions concerning consumer health and food safety related to production, processing and supply of food of animal origin. The SCVPH reviewed all the old and new data and issued its opinion on 30 April 1999, which it reviewed and confirmed again in 2000 and once more in 2002 on the basis of additional and new information submitted subsequently.

4.67 Based on this comprehensive risk assessment, the European Communities adopted Directive 2003/74/EC. In accordance with the above scientific conclusions the Directive provides for a definite import prohibition on meat and meat products from animals treated for growth promotion purposes with oestradiol-17β. Furthermore, on the basis of the available but still incomplete data, the Directive provides for a provisional ban on meat and meat products from animals treated for growth promotion purposes with testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate. The Directive provides for an obligation on the Commission to seek more complete scientific information from any source which could shed light and clarify gaps in the present state of knowledge on these substances.

4.68 Article 22.8 of the DSU obliges Canada to cease applying the suspension of concessions, once an inconsistent measure has been removed. However, even though the inconsistent measure has been removed, Canada continues to apply the suspension of concessions. Canada, therefore, is in violation of Article 22.8 of the DSU.

(b) Canada is in violation of Articles I and II of the GATT 1994 following the continued application of suspension of Concessions

4.69 The illegal continued suspension of concessions and related obligations automatically entails a violation of Articles I and II of the GATT 1994. This has been explained above to which the European Communities would refer to.

D. FIRST WRITTEN SUBMISSION OF CANADA

1. Introduction

4.70 This case involves three issues. First, it is about whether the DSB authorization permitting Canada to suspend concessions with respect to the EC – in response to the EC's failure to comply with the recommendations and rulings of the DSB in the *EC – Hormones* dispute – remains in effect. Second, it is about whether the EC bears the burden of demonstrating that it has complied with those recommendations and rulings in order to have the DSB authorization terminated. And third, it is about whether the EC has actually complied with those recommendations and rulings. The first two issues must be answered in the affirmative; the third issue must be answered in the negative.

2. Background to the dispute

4.71 The EC has had in place since the 1980s a ban on the importation of meat and meat products derived from cattle treated with any of six growth-promoting hormones. In the *EC – Hormones* dispute, the DSB ruled that EC legislation implementing the ban (*i.e.* Directive 96/22/EC) was not

based on a risk assessment as required by the *SPS Agreement.* The DSB, in February 1998, recommended that the EC bring its measure into compliance and was subsequently granted fifteen months to do so. The EC failed to comply within that time and as a result the DSB, in July 1999, authorized Canada to suspend concessions to the EC to the amount of Can$11.3 million. On the basis of that authorization, Canada adopted the *European Union Surtax Order*, a measure which remains unchanged and in force to this day.

4.72 After having been found non-compliant in the *EC – Hormones* dispute, the EC commissioned a series of scientific studies and mandated the SCVPH to review these studies along with other available scientific evidence. The SCVPH produced three opinions, in which it concluded that a "risk to the consumer has been identified with different levels of conclusive evidence for the 6 hormones in question." The opinions concluded that oestradiol-17β is a "complete carcinogen", that the current state of knowledge does not allow a quantitative estimate of the risk for the other five hormones, and that no ADI could be established for any of the six hormones.

4.73 On the basis of the three SCVPH opinions, the EC adopted Directive 2003/74/EC in September 2003. This Directive simply amended Directive 96/22/EC by making the ban on oestradiol-17β permanent, on the ground that it was now based on a risk assessment, and by making the ban on the other five substances provisional, on the ground that there was insufficient information to complete a proper risk assessment.

4.74 Upon notifying its amended Directive to the DSB, the EC stated that it considered itself in compliance with the recommendations and rulings in the *EC – Hormones* dispute and, as a result, Canada's suspension of concessions was no longer justified. Canada responded that it was for the EC to obtain multilateral confirmation of its claim of compliance, and explained that Canada's continued suspension of concessions was pursuant to the original and continuing DSB authorization. Canada further questioned how the EC's notification to the DSB of its unilateral assertion of compliance could terminate Canada's multilateral authorization.

4.75 The EC did not initiate WTO compliance proceeding or otherwise seek confirmation from the DSB of the compliance of its measure. Instead, it requested the establishment of this Panel, alleging that it was Canada's continued suspension of concessions that was inconsistent with Articles I and II of GATT 1994 and Articles 23.1, 23.2(a) and (c), 3.7, 22.8 and 21.5 of the DSU.

3. Legal arguments

4.76 This dispute concerns the respective rights and obligations under the DSU of the EC and Canada in the context of Canada's adoption of WTO-authorized suspension of concessions to the EC. This dispute also concerns the obligations of the EC under the *SPS Agreement*, in particular, whether the EC has actually complied with the recommendations and rulings of the DSB in the *EC – Hormones* disputes.

(a) Canada has not acted inconsistently with Articles 22.8 and 3.7 of the DSU

4.77 In alleging that Canada has acted inconsistently with Articles 22.8 and 3.7 of the DSU, the EC fails to acknowledge that: 1) the DSB authorization permitting Canada to suspend concessions remains in effect; 2) it is the EC, and not Canada, that now bears the burden of demonstrating that its measure now complies; and 3) the EC measure does not benefit from a presumption of compliance in these circumstances.

(i) The DSB authorization remains in effect

4.78 The EC's claim that its unilateral assertion of its own compliance has resulted in the automatic termination of Canada's authorization to suspend concessions must fail. That authorization remains unchanged and in effect to this day. The EC remains subject to an ongoing obligation to comply with its WTO obligations. Moreover, the *EC – Hormones* dispute has remained at all times under the surveillance of the DSB, including the EC's obligation to comply as well as the suspension of concessions by Canada that was authorized to induce this compliance.

4.79 Canada's measure is therefore by definition WTO consistent and only the DSB can terminate the authorization of that measure. Any mechanism for terminating the authorization that is not under the authority and surveillance of the DSB undermines the ability of the dispute settlement system to achieve one of its central objectives, that of ensuring the security and predictability of the multilateral trading system.

(ii) The EC bears the burden of demonstrating its compliance

4.80 It is the EC, and not Canada, that bears the burden of demonstrating that it has complied with the recommendations and rulings of the DSB. As explicitly recognized by the panel in *US – Certain EC Products*, this proposition flows from the general rules on burden of proof. That is, since it is the EC that seeks to have Canada's authorized and WTO-consistent measure "de-authorized", it is the EC that bears the burden of demonstrating that the measure should no longer be authorized on the basis of the actual compliance of its own measure.

4.81 It is therefore incumbent upon the EC to avail itself of the avenues available to it under the DSU to demonstrate that it has complied with the recommendations and rulings of the DSB, with a view to having the DSB authorization revoked. The EC may have recourse to proceedings initiated under Article 21.5 or it may initiate new proceedings in which it requests the Panel to deliver findings on the actual compliance of the EC measure. Under either scenario, Canada's continued suspension of concessions remains WTO-authorized, WTO-consistent and unchallengeable until such time as the EC successfully demonstrates the compliance of its own measure, and consequently the DSB terminates the authorization concerned.

(iii) The EC measure does not benefit from a presumption of compliance

4.82 Relying upon an unfounded assertion that its measure benefits from a presumption of compliance, the EC claims that it has satisfied the first condition of Article 22.8 of the DSU by "removing" its measure. As a result, according to the EC, the temporary period provided for in Article 22.8 has passed and Canada's DSB authorization has been automatically terminated. Canada does not challenge the existence and correctness of a presumption of good faith in many circumstances, nor does it disagree that authorized suspension of concessions is meant to be temporary. However, neither of these principles is relevant in the circumstances of this dispute.

4.83 Underlying this dispute is neither an EC measure taken as part of its day-to-day business of governing, nor one that the EC has taken to comply prior to the adoption of DSB authorization to suspend concessions. Rather, this dispute concerns the failure of the EC to correct a measure that had been found by the DSB to be inconsistent with the EC's WTO obligations, and as a result the DSB authorized Canada to suspend concessions. The existence of DSB authorization, and the adoption by Canada of a measure based on that authorization, distinguishes this case from those situations in which a presumption of compliance might apply to the EC measure.

4.84 The DSU does not explicitly address how a DSB authorization of suspension of concessions, once granted, is to be terminated. What is clear is that the EC's unilateral claim of compliance cannot,

in itself, terminate that authorization. Any presumed compliance the EC measure might enjoy prior to the adoption of the DSB authorization must yield to the actual compliance of Canada's WTO–authorized measure. Any other interpretation of the DSU would undermine the objective of the dispute settlement system to ensure the security and predictability of the multilateral trading system.

4.85 If the EC's claims were to be accepted, both meritorious and purely illusory claims of compliance would result in the immediate termination of the suspension of concessions, even if the assertions of compliance were patently unreasonable. An otherwise WTO-consistent measure (*i.e.* suspending concessions) of one Member would be automatically rendered WTO-inconsistent by the simple adoption and notification of a "compliance measure" by another Member. The self-proclaimed "complying" Member could buy itself considerable periods of relief through the announcement of a measure that barely differed from the one originally found to be non-compliant. This scenario would clearly not contribute to the objectives of inducing prompt compliance and ensuring the security and predictability of the multilateral trading system.

4.86 The EC's claims under Article 3.7 of the DSU – which are coincidental to its claims under Article 22.8 – also fail as Canada has demonstrated that it has not acted inconsistently with Article 22.8.

(b) Canada has not acted inconsistently with Articles 23.1, 23.2(a) and 21.5 of the DSU

4.87 The EC also claims that: 1) Canada is seeking to redress a perceived WTO violation without recourse to the rules and procedures of the DSU, contrary to Article 23.1 of the DSU; 2) Canada has made a unilateral determination that the EC's current measure is not in compliance with the recommendation and rulings of the DSB, contrary to Article 23.2(a) of the DSU; and 3) Canada's failure to initiate compliance proceedings to determine the WTO consistency of the EC's current measure is contrary to Article 21.5 of the DSU. These claims are unsustainable.

(i) Canada is not seeking redress of a perceived WTO violation

4.88 The EC's claim that Canada has sought to redress a perceived violation without recourse to the rules and procedures of the DSU is based on a misunderstanding of the basis for Canada's continued suspension of concessions. The panel in *EC – Commercial Vessels* found that a necessary precondition to the application of Article 23 of the DSU is that a Member must be acting in response to the perceived WTO-inconsistent behaviour of another Member. In the circumstances before this Panel, Canada is not seeking the redress of a perceived WTO violation; it has already sought and obtained redress pursuant to the rules and procedures of the DSU.

4.89 In the *EC – Hormones* dispute, Canada sought and obtained DSB authorization to suspend concessions to the EC after the EC failed to bring itself into compliance with the recommendations and rulings of the DSB within the reasonable period of time. Canada's impugned measures were adopted and continue to be applied pursuant to this validly obtained authorization from the DSB, and not on the basis of any views it has subsequently developed on the consistency of the EC's current measure. In other words, Canada's assessment of the consistency of the EC's current measure is unrelated to, and irrelevant to, Canada's continued suspension of concessions.

(ii) Canada has not made a unilateral determination

4.90 The EC is simply wrong to suggest that Canada's continued suspension of concessions necessarily implies that it has made a unilateral determination that the EC measure does not comply. According to the text of Article 23.2 itself, as well as the Appellate Body in *US – Certain EC Products*, that provision simply sets out certain specific and clearly-defined forms of unilateral action

already prohibited "in such cases" covered by Article 23.1. Since Canada is not seeking to redress a perceived violation, it cannot be said to have made a unilateral determination.

4.91 Moreover, the panel in *US – Section 301 Trade Act* found that a "determination" can only occur subsequent to a Member having decided that, in its preliminary view, there may be a WTO inconsistency. Mere opinions or views expressed before that stage is reached are not intended to be covered by Article 23.2(a). In the circumstances in this dispute Canada has not passed this threshold of having made a "determination" regarding the EC's current measure.

4.92 In support of its allegations that Canada has made such a determination, the EC has incorrectly interpreted statements made by Canada in the DSB. The reality is that Canada consistently stated that it is the EC's responsibility to establish that it has complied with the DSB's recommendations and rulings, and as result there was no reason for Canada to initiate WTO procedures or to take any other action. The views that Canada expressed on the WTO consistency of the EC's current measure are unrelated to, and irrelevant to, its continued suspension of concessions.

(iii) Canada has no obligation to initiate compliance proceedings

4.93 The EC's allegations that Canada was under an obligation to initiate compliance proceedings under Article 21.5 of the DSU must also fail, as these allegations are based on unfounded assertions that Canada is seeking redress of violation and that it has made a unilateral determination. The mechanism of Article 21.5 was available to either party to obtain a determination as to whether the EC's measure is in compliance. However, it is the responsibility of the EC to avail itself of this procedure if it wishes to have the ongoing DSB authorization terminated.

4.94 The EC's own failure to initiating proceedings under Article 21.5 of the DSU is not a legitimate basis for a claim that Canada acted unilaterally by not initiating such proceedings. Nor does it absolve the EC of its responsibility to demonstrate that it has brought itself into compliance. The EC's interpretation of the DSU on this point, were it to prevail, would negate a WTO Member's right to rely on a validly obtained DSB authorization to suspend concessions and would seriously undermine the proper functioning of the dispute settlement system in the WTO. Furthermore, the DSU cannot be interpreted to compel a Member to initiate proceedings to challenge another Member's measures.

4.95 The EC also incorrectly considers Canada's submission in *US – Section 301 Trade Act* as contradicting its position in these proceedings. The circumstances on which Canada was commenting in that case were very different from those before this Panel. That dispute concerned a US law allowing the US to impose retaliatory measures without having obtained multilateral authorization for such measures. Canada agrees that WTO Members should have recourse to the WTO dispute settlement system rather than their own unilateral determinations. In the current case, however, Canada's measure has been adopted pursuant to DSB authorization and the EC's unilateral and unconfirmed declaration of compliance cannot create a positive obligation for Canada to initiate proceedings under Article 21.5 of the DSU.

(c) The EC has failed to demonstrate its compliance with the recommendations and rulings of the DSB in *EC – Hormones*

4.96 Canada has demonstrated that the EC measure does not benefit from a presumption of compliance in these circumstances and that the EC bears the burden of demonstrating that it actually complies. It has failed to do so. What the EC has put forward in respect of its own measure is three paragraphs from the recitals of Directive 2003/74/EC that summarize the conclusions of the SCVPH. This falls far short of a prima facie case of compliance with the recommendations and rulings of the DSB in *EC – Hormones*.

4.97 The Appellate Body in *US – Gambling* found that a prima facie case must be based on "evidence *and* legal argument" put forward by the party making a claim. It is insufficient therefore for the EC to simply submit limited evidence and expect the Panel to divine from it the EC's claim of compliance. Nor can the EC simply allege facts without relating them to arguments about how they demonstrate compliance. When one assesses the EC's three paragraphs in the light of criteria established by the Appellate Body, it is clear that the EC has failed to establish even a prima facie case of compliance.

(d) Arguments and evidence concerning the non-compliance of the EC measure

4.98 The Panel should dismiss this case on the grounds that the EC has failed to make its case in respect of allegations that Canada has acted inconsistently with the DSU. Canada is nonetheless prepared to elaborate on arguments and scientific evidence that the EC measure does not comply with the recommendations and rulings of the DSB in *EC – Hormones*, an issue the EC is trying to avoid.

(i) The EC's permanent ban on oestradiol-17β is not based on a risk assessment

4.99 The EC has not met either of the two conditions required to demonstrate that its permanent ban on oestradiol-17β is based on a risk assessment. The EC must demonstrate that the SCVPH Opinions constitute a "risk assessment" and that the EC measure banning the use of oestradiol-17β for growth-promotion purposes is "based on" that risk assessment.

(e) The SCVPH Opinions do not constitute a risk assessment

4.100 With respect to the first condition, the Appellate Body in *EC – Hormones* set out a two-step process that the SCVPH Opinions must follow to be considered a risk assessment for the purposes of the *SPS Agreement*. The SCVPH Opinions must first identify the adverse effects on human health (if any) arising from the presence of the six hormones when used as growth promotants in meat and then, if any such adverse effects exist, they must evaluate the potential occurrence of these effects. They do neither.

4.101 First, the SCVPH opinions do not identify any adverse effects on human health that arise from the consumption of meat containing residues of oestradiol-17β that has been used as a growth promotant. The SCVPH opinions identify only in a speculative fashion potential adverse effects of oestradiol-17β in general, a substance available from many sources both internal (endogenous) and external (exogenous) to the human body.

4.102 None of the potential adverse effects identified by the SCVPH were said to arise specifically from the consumption of meat containing residues of oestradiol-17β when used as a growth promotant. In fact, the SCVPH specifically acknowledges the absence of such a link. As a result of the speculative nature of the identification of potential adverse effects in general and the absence of a specific link between such effects and the use of hormone growth promotants in particular, the SCVPH opinions cannot be seen to satisfy the first step in the conduct of a "risk assessment".

4.103 Second, the SCVPH Opinions do not evaluate the potential occurrence of the adverse effects they purport to identify. The three SCVPH opinions simply point to general concerns about possible adverse effects of oestradiol-17β, and do not evaluate the potential occurrence of such effects as a result of consumption of meat derived from hormone-treated animals. Moreover, the SCVPH has failed to conduct even the minimum steps of such an evaluation.

4.104 The Appellate Body found in *EC – Hormones* that the scientific evidence considered in a risk assessment had to be "sufficiently specific" to the substance at issue. Even those potential adverse effects that it does identify the SCVPH does not evaluate in a manner that is sufficiently specific to

the substances at issue, and as such the SCVPH has not completed the second step required of a risk assessment.

(f) The EC measure is not based on a risk assessment

4.105 With respect to the second condition, the EC measure is not based on a risk assessment. Since the EC has not even conducted a proper risk assessment, the measure cannot be said to be "based on" a risk assessment. However, even if the SCVPH opinions are considered to constitute a risk assessment, the EC still fails to satisfy this condition as its measure is not "based on" that risk assessment.

4.106 The Appellate Body in *EC – Hormones* found that the results of the risk assessment must "sufficiently warrant" an SPS measure, and there must be a "rational relationship" between the measure and the risk assessment. In order to satisfy this test, the EC must demonstrate that the conclusions of its so-called risk assessment (that oestradiol-17β in general may have adverse effects) sufficiently warrant the conclusions underlying its measure (that residues of oestradiol-17β consumed from meat derived from animals treated for growth-promoting purposes have adverse effects).

4.107 All that the SCVPH has arguably identified are some potential adverse effects associated with oestradiol-17β *per se*. It has not demonstrated that these adverse effects occur as a result of consumption of the quantity of oestradiol-17β that would be present in meat derived from treated animals. Even if the conclusions on the adverse effects of oestradiol-17β were correct, the rational response would be to ban oestradiol-17β, or at least to inform consumers of its various sources and the actions they should take to minimize exposure. The EC has instead chosen to respond to advice about the potential adverse effects of oestradiol-17β from all sources by banning only meat from animals treated with oestradiol-17β for certain purposes, while allowing others.

4.108 In *EC – Hormones*, the EC failed to convince either the panel or the Appellate Body that its measure – which was nearly identical to the present one – was "based on" on a risk assessment. The evidence that the EC now relies on remains as insufficient to establish a basis for its ban as it was in *EC – Hormones.* As a result, the conclusions of the SCVPH opinions do not support the conclusions underlying the measure, so the measure is not "based on" a risk assessment.

(i) The EC's ban on the five other hormones is not a provisional measure

4.109 The EC claims that its provisional ban on five other hormones – testosterone, progesterone, TBA, zeranol and MGA – is justified under Article 5.7 of the *SPS Agreement*, on the ground that there is insufficient scientific knowledge to conduct a risk assessment. As the EC has failed to present any evidence in support of this claim, it must also fail. In fact, the EC expressly stated in *EC – Hormones* that its ban on these hormones was not a provisional measure in the sense of Article 5.7, presumably because it concluded that there was sufficient scientific information on which to base its measure at the time. It strains credulity therefore for the EC to now assert, over seven years later, that the ban on these hormones is now being imposed on a "provisional" basis.

4.110 The burden of proof rests on the party invoking Article 5.7 to justify its provisional measure to make a prima facie case in support of that position. The EC has failed to present any case whatsoever in support of its provisional ban, choosing instead to merely cite Directive 2003/74/EC in support of its contention that its ban is a provisional measure. Regardless of where the burden lies, there is ample evidence to suggest that the EC has no grounds for justifying the ban on these five hormones on a provisional basis.

4.111 In interpreting the obligations under Articles 2.2 and 5.7 of the *SPS Agreement*, the Appellate Body in *Japan – Agricultural Products II* set out four cumulative requirements for a measure to be

justified as a provisional measure. A measure may be justified as "provisional" where: (1) it is imposed in a situation where relevant scientific evidence is insufficient; (2) it is adopted on the basis of available pertinent information; and such a provisional measure may only be maintained where: (3) the Member seeks to obtain additional information necessary for a more objective assessment; and (4) the Member reviews the measure accordingly within a reasonable period of time.

4.112 With respect to the sufficiency of the scientific evidence, the body of scientific evidence relating to these five hormones is such that the EC cannot plausibly argue that it is insufficient to conduct a proper assessment of risk. The five hormones have already been the subject of several risk assessments by reputable national regulatory agencies and international expert scientific committees, such as JECFA. In fact, the panel in *EC – Hormones* found that several scientific reports met the minimum requirements of a risk assessment.

4.113 JECFA's studies of these five hormones reveal the breadth and depth of the available scientific evidence. As early as 1981, JECFA evaluated the health effects of residue levels of progesterone and testosterone, concluding that residues from the use of these hormones according to good veterinary practices are unlikely to pose a hazard to human health. After its most comprehensive evaluation in 1999, JECFA recommended ADI levels for these two hormones. In 2000, JECFA published residue and toxicological monographs, in which it referenced a large number of available studies dealing with progesterone and testosterone. Zeranol and TBA were considered by JECFA in 1982 and again in 1983. JECFA ultimately recommended an ADI for zeranol in 1987 and one for TBA in 1989. JECFA then turned its attention to MGA in 2000 and again in 2004, at which time it recommended an ADI.

4.114 In the light of the available scientific evidence on which JECFA has based it recommendations, it is clear that JECFA does not consider that residues of these hormones have an adverse effect on human health, provided they are used in accordance with good veterinary practices. Faced with this conclusion from JECFA, the EC cannot substantiate its assertion that there is insufficient scientific information to perform an adequate risk assessment in respect of these five hormones.

4.115 With respect to the availability of pertinent information, the Panel would only need to consider this second requirement in the event that it accepted that there is insufficient scientific evidence to allow the EC to conduct an adequate risk assessment. If the Panel proceeds to this stage, the requirement that a measure be adopted "on the basis" of available pertinent information requires that there be a rational relationship between the EC measure and the available pertinent information. An objective analysis of the available pertinent information regarding the health risks associated with residues of these hormones does not reasonably support the EC's ban on these five hormones.

4.116 The EC's ban is inconsistent with the current position of JECFA and Codex – an organization specifically recognized in the *SPS Agreement* as an international standard-setting body – on the human safety of these hormones when used in accordance with good veterinary practices. JECFA concluded that there was no need to specify numerical MRLs for progesterone and testosterone when these substances are used in accordance with good veterinary practices. JECFA recommended MRLs for zeranol, TBA and MGA in 1987, 1989 and 2004, respectively. For its part, Codex indicated in 1995 that it was "unnecessary" to set numerical MRLs for progesterone and testosterone. It did set numerical MRLs for zeranol and TBA.

4.117 Finally, with respect to the third and fourth requirements under Article 5.7 – the collection of additional information for a more objective assessment and review within a reasonable period of time – the EC has not demonstrated that it is complying with these obligations. Although the EC Directive specifically indicates that the Commission shall seek additional information from all

possible sources, the EC has provided no evidence of its efforts to obtain the necessary information to conduct a proper risk assessment.

(g) Canada has not acted inconsistently with Articles I and II of the GATT 1994

4.118 Canada's suspension of obligations is authorized by the DSB and therefore fully justified under the DSU. Since the EC's claims under Articles I and II of the GATT 1994 are dependent on its DSU claims, these consequential claims must also fail.

E. ORAL STATEMENT OF THE EUROPEAN COMMUNITIES DURING THE FIRST SUBSTANTIVE MEETING

1. Introduction

4.119 The central provision on which the European Communities bases its claims is Article 23 of the DSU. Article 23 requires WTO Members to have recourse to the procedures set out in the *DSU* instead of resorting to any kind of "self-help." Article 23, in other words, prohibits a WTO Member from making itself the judge over other WTO Members. What is and what is not a violation of the covered agreements and what one can do to remedy it, are to be determined multilaterally, not unilaterally.

2. Seeking redress – Article 23.1

4.120 As to Article 23.1 all parties seem to agree that when, in 1999, the US and Canada requested, obtained and started using a DSB authorization to suspend concessions, they were seeking to redress a violation established at that time. The parties differ on what the US and Canada are doing right now. One should think that they are still seeking redress. After all, they are still applying their suspension of concessions stating explicitly that they fail to see how the European Communities' implementation measure achieves compliance. This can only mean that they still see a violation, especially given that Article 22.8 of the DSU would prohibit the continuation of sanctions in the opposite case.

4.121 The defending parties, however, flatly deny that what they are doing right now is seeking redress of a violation against an alleged WTO-inconsistency of the implementing measure. The United States states that it "has already sought and obtained redress through the multilateral dispute settlement system for a violation found by the DSB." Canada not only uses the same terms – "sought and obtained" – but also takes the trouble of underlining those words in its submission in order for everyone to understand the difference between the present tense ("seeking"), in Article 23.1 DSU, and the past tense of "sought and obtained". That difference seems obvious enough. What is much less obvious, however, is how, by referring to the past, the defending parties want to explain what they are doing right now. Applying sanctions is a form of seeking redress as the defending parties have admitted themselves. They are currently applying sanctions – present tense, not past tense – so how could they not be seeking redress?

4.122 They are not seeking redress, so the defending parties say, because they are acting under an authorization. An authorization, however, can neither deny facts nor derogate from a Member's obligations outside its scope. Thus, as regards specifically Article 23 of the DSU, it is clear that the mere existence of an authorization cannot simply do away with the obligation to abide by the rules and procedures of the DSU, when a Member is seeking redress of a violation.

3. Article 23.2(a) of the DSU in conjunction with Article 21.5 of the DSU

4.123 As regards specifically the EC's claim under Article 23.2(a) in conjunction with Article 21.5 the defending parties put forward a number of reasons as to why there is no determination by them.

Interestingly enough, they hardly deal with one of the main points the European Communities has raised, namely that their "unilateral determination" can be inferred from the fact that they continue to apply sanctions unilaterally. And how could it not be inferred from it? It is inconceivable – and indeed would be even worse than what we are discussing now – if they did so without any good reason. On the other hand, both spend considerable time in their first written submissions explaining – in a rather defensive manner – that their public statements do not constitute determinations, that they never alluded to a violation, that they have not yet concluded on non-compliance, etc. And finally, elsewhere in their submissions, they spend even more time explaining why the European Communities' implementing measure actually falls short of compliance.

4.124 Whether or not a specific statement reaches – as Canada puts it – the "threshold" of a determination is one thing. Yet, another thing is if that statement is accompanied by conduct that severely affects the EC's trade. We are not looking at statements made *in abstracto* here. A "determination" need not be pinned down to a specific statement in a specific form, it is the whole conduct a WTO Member is displaying that needs to be looked at.

4.125 The defending parties further claim that they do not have an obligation under Article 21.5 of the DSU to launch compliance proceedings. This Panel, however, is asked to find whether, under Article 23 of the DSU, in conjunction with Article 21.5, a Member has an obligation to launch a compliance procedure if and because it continues to apply sanctions against another Member, even though there is a new implementing measure. It is not relevant for this dispute what obligations can be found directly in 21.5 in the absence of such unilateral conduct.

4.126 Finally, the United States claims that there is no obligation for the complaining parties to *immediately* launch a compliance review. In the present context and circumstances, with almost one and a half years that have passed after the adoption of the European Communities' implementing measure at the moment when this Panel was established and with all the discussions that took place between the parties to this dispute regarding this implementing measure, both before and after it was adopted, the question of how quickly a retaliating complainant must react to an implementing measure does not pose itself. If anything, one could discuss the defendants' bad faith and their contradictory behaviour (*venire contra factum proprium).*

4. Article 23.1 in conjunction with Articles 22.8 and 3.7 of the DSU

4.127 As regards the EC' claim under Article 23.1 in conjunction with Article 22.8, 3.7 of the DSU, the defending parties submit that the conditions of Article 22.8 are not fulfilled because the European Communities did not prove that it has "removed" the inconsistency of the measure. This argumentation overlooks the fact that dispute settlement proceedings are about a non-compliance review not a compliance review. Indeed, in all dispute settlement proceedings that have ever been adopted by the DSB it was for a complaining Member to prove the WTO *in*consistency of a measure by another Member. This is explicitly confirmed by Article 6 of the DSU, the provision under which panels are established.

4.128 The defending parties ignore that the European Communities makes its systemic claim under *Article 22.8, in conjunction with Article 23.1.* Thus, the Panel is called upon to decide whether or not the conditions under Article 22.8 are fulfilled *in view of* the prohibition under Article 23 to make unilateral determinations of non compliance. It is not possible for the defending parties to contest the removal by the EC of the inconsistency of our old measure (Article 22.8), without making a unilateral determination under Article 23.

4.129 Further, both defending parties submit that the European Communities cannot base itself on a presumption of good faith compliance. The European Communities bases itself on the same *rationale* as the Appellate Body in the *Byrd Amendment* case. Thus, even though the defending parties allege

that the European Communities is still in violation of the *SPS Agreement*, this does not in any event affect the presumption of good faith. As the Appellate Body has made clear, these are two completely different questions.

4.130 The defending parties claim that there is a reversed burden of proof in a compliance case. Contrary to what Canada believes, a reversal of presumption can also not be deduced from the DSB authorization granted in 1999. The DSB authorization is limited to giving a Member the right to apply sanctions. However, it does not go further than that. The DSB authorization cannot reverse the normal rules which apply for subsequent implementing measures.

4.131 If Canada's criterion of a "day-to-day business" conduct for the presumption of good faith should bear any relevance at all, the European Communities considers that in the present case it even supports the EC' reliance on good faith. Indeed, the European Communities prepared the implementation of the DSB recommendations and rulings with extraordinary carefulness. During the compliance process, the European Communities has made every effort to analyse the relevant scientific evidence in full transparency and with an open mind. All stakeholders – whether inside or outside the European Communities – had at every moment in time the opportunity to submit relevant information and to intervene in the whole process.

4.132 It is therefore also absurd, and indeed puts the reality on its head, to maintain that the European Communities in this case seeks to end the sanctions on the basis of a "mere declaration of compliance", and that this could be done also just "a week after" the DSB authorization. It insinuates that the European Communities abused its rights and it just waives its hand to claim compliance. In the light of the whole process, as just described, it is instead fully legitimate for the European Communities to rely on the presumption of good faith for its compliance.

4.133 As to the relevance of the DSB authorization for the continued application of sanctions in the context of Article 22.8, obviously, the defending parties and the European Communities have different views about the scope of the DSB authorization. For the United States and Canada, the DSB authorization operates like a sort of "absolute justification" which makes every behaviour *per se* WTO consistent, irrespective of any subsequent events and compliance acts. On the other hand, the European Communities considers that it is necessary to put the DSB authorization in its proper context under the DSU.

4.134 In this case, the DSB authorization has been granted under Article 22.7 following an arbitration procedure under Article 22.6 of the DSU. The subject-matter of this Article 22.6 arbitration was the level of nullification or impairment caused by the original EC's Hormones legislation. Thus, it is crucial to note that the very basis of the DSB authorization has been the WTO-inconsistency of the Member *before* the authorization was granted. On the other hand, the DSB authorization is not based on any (alleged) WTO inconsistency of a compliance measure that has been adopted *afterwards*.

4.135 What follows from this important and undisputable fact is that, first of all, in case of a subsequent compliance that is properly adopted and duly notified to the WTO, the basis on which the DSB has granted its authorization has fundamentally changed. The DSB only granted the authorization to suspend concessions precisely because a WTO Member had been found to be WTO inconsistent in the past and no implementation measure was taken within the reasonable period of time. The DSB's authorization was to induce compliance by the other Member and to rebalance temporarily the rights and obligations until the other Member has complied.

4.136 Second, the DSB authorization is even more fundamentally changed in case of a subsequent compliance measure which has never been found WTO-inconsistent, because the defending parties do not dare to challenge it under Article 21.5. In its first written submission, the European Communities

has referred to the "sequencing" discussion and practice of WTO Members in case of a compliance act before the DSB authorization is granted. Quite remarkably, in the *EC – Bananas III* dispute, the DSB Chairman explicitly stated that the sequencing of a determination of compliance or non-compliance and the suspension of concessions should be treated in a "logical way forward".[17]

4.137 As it happened, the logical way forward at the time was to assess first whether or not the compliance measure was sufficient before determining the nullification or impairment caused by the WTO-inconsistent measure. In stark contrast to this sequencing, the defending parties consider now that the logical way forward is to continue to apply sanctions even though the EC' compliance measure has not been challenged by them and not been found WTO-inconsistent. And what is more, they even refuse to challenge the EC' compliance measure pretending that this is not necessary since they have a DSB authorization.

4.138 But how can Canada and the United States know that the European Communities is still not in compliance with its obligations? They do so solely on the basis of a unilateral determination of the EC' compliance measure which is in obvious contradiction to Article 23 and Article 21.5 of the DSU.

4.139 One might argue that the DSU is not explicit on this question. However, the DSU contains several elements which indicate that the DSB authorization can not serve as a blank cheque for the continuous application of the sanctions even after a subsequent compliance measure has been adopted and notified properly to the DSB.

4.140 First, let us consider the wording of Article 22.8 of the DSU and what it does *not* say. Even in case of a removal of the inconsistency of the measure, Article 22.8 does *not* say that the "DSB authorization ceases to apply". Instead, it states that the suspension of concessions or other obligations shall not "be applied" any longer. Thus, Article 22.8 does not formally address the fate of the DSB authorization. In an Article 22.8 situation it is, therefore, perfectly conceivable that although the DSB authorization is not *formally* terminated or withdrawn, a WTO Member is not entitled to continue the application of suspension of concessions. Furthermore, Article 22.8 does *not* say that the removal of the inconsistency or the termination of the application of suspension requires whatever kind of DSB decision. Rather, Article 22.8 is self-executing. The use of the word "shall" supports this interpretation, which does not give any margin of manoeuvre and requires no additional acts.

4.141 Second, contextually, Article 22.8 describes the next procedural step in the course of a dispute after an authorization has been granted. Article 22.8, therefore, provides for the next logical step. Consequently, once the inconsistency of the measure has been removed, the application of suspension of concessions or other obligations is no longer permitted.

4.142 In addition, Article 22.8 should be interpreted in the context of Article 23 of the DSU, which prohibits WTO Members from judging unilaterally the properly adopted and notified compliance measures of other WTO members. According to the text, object, purpose and context of Articles 22.8 and 23, the defending parties must seek a determination of non-compliance under the normal DSU procedures. This general principle is not altered in whatever way under Article 22.8.

4.143 Another contextual element which should be taken into account is Articles 3.7 and 22.1 of the DSU, which underline the exceptional and temporal nature of the application of suspension of concessions or other obligations. Their exceptional and temporal nature effectively complements the principle of good faith. In case of a properly adopted and notified compliance measure, the exceptional and temporal justification of countermeasures is put into question. In the presence of a subsequent compliance measure, the "normal" situation revives and sanctions can no longer be applied as if nothing has changed.

[17] Minutes of the DSB Meetings held on 25, 28 and 29 January and 1 February 1999, WT/DSB/M/54.

4.144 Canada tries to draw contextual support for its position from Article 3.2, emphasizing the security and predictability given by the DSB authorization. The "security and predictability" under Article 3.2, also applies to the WTO Member who properly implements its obligations. Once this Member has removed the inconsistency of the measure it should have the reassurance that sanctions are no longer applied. At a minimum, the implementing Member must have the reassurance that its measure is properly challenged under the DSU by the retaliating Member, which does not agree with the compliance measure. But even this, Canada and the United States refuse to do despite the repeated requests by the European Communities to do so.

4.145 The European Communities would also recall the object and purpose of the trade sanctions, which is to induce compliance and to rebalance the rights and obligations under the WTO agreements. However, both objectives require that a Member's measure has been found first to be WTO-inconsistent in accordance with the DSU rules. And such a determination concerns logically not just any measure, but the measure that is currently in force in the Member concerned. Transposed in the present context, it means that Canada and the United States cannot simply argue that the "old" measure has been found to be WTO-inconsistent in 1998. This measure is not any longer in force, since the European Communities adopted and notified its compliance measure in 2003. It is simply not rational and credible to argue that the object and purpose of the suspension of concessions continues to exist, if its basic reason, i.e. the old WTO-inconsistency, has disappeared.

5. Concluding statement of the European Communities

4.146 The EC believes that allowing public observation of the debate during this hearing has been very beneficial for the public's understanding of the dispute settlement process as well as this particular dispute. The public observation has in no way hindered an efficient conduct of this hearing. On the contrary, the third parties have clearly benefited from their observation of this hearing during the first two days for the purpose of their participation in this dispute.

4.147 What we have heard from the defendants in the last few days is essentially that a retaliating Member has no obligation whatsoever under the DSU. Instead, the retaliating Member may continue to apply sanctions until the authorization is "revoked" by the DSB. The United States and Canada argue that by virtue of this authorization they can simply lean back and see what the complying Member comes up with. If eventually the complying Member adopts an implementation measure they do not even see a need to review it in due time. Let me remind that in this case the United States and Canada claim that they have even after two years (and I should add after an additional three years of preparation) not made up their mind whether the EC's measure is WTO consistent. Indeed there seems to be no prospect that the United States and Canada will ever make up their minds. Canada has stated that it would never make a determination about the EC's new measures and the United States gave even less cause for reassurance stubbornly refusing even to agree that there is a disagreement.

4.148 Whatever the defendants may mean by these statements, it is clear that the United States and Canada do not accept a responsibility to submit the EC's legislation to a multilateral review as it has been done in any other case by WTO Members which ended in an adopted WTO decision. And although they do not contest that the EC has acted in good faith, they do not even concede that the EC's measure can benefit from a presumption of good faith compliance.

4.149 This is a very easy going way for the United States and Canada. But it cannot be the correct one under the DSU.

4.150 The EC would recall some essential points which had been discussed by the parties:

4.151 First, the EC has advanced what would be the logical solution to this dispute, i.e. to follow its example in the *US – FSC* case (launching Article 21.5 compliance procedure by original complaining

party, suspension of sanctions in the meantime). Quite remarkably, the United States fully agreed with this EC' approach and considered it as "the appropriate solution" in the *US – FSC* dispute. Yet, the EC struggles to understand why in a reverse situation where the United States is retaliating, the United States does not follow this example if it considers it as "appropriate".

4.152 Second, there has been a lot of discussion about the presumption of good faith and the presumption of compliance, which is important for the EC claim under Article 22.8 and Article 23.1 of the DSU. Neither the United States nor Canada nor any of the Third Parties have contested that the EC has adopted its compliance measure in good faith. Yet, the United States and Canada refuse that the EC may rely on this principle in a "post-implementation" scenario. The United States even wants to go as far as to say that the principle of good faith is not part of the DSU. Obviously, this view is contrary to what the Appellate Body has constantly ruled but also irreconcilable with general principles of public international law. Moreover, when we asked Canada about the basis in the DSU of its assumption that an implementing Member faced with retaliation is not entitled to this presumption, it could not provide any answer. Indeed, this is so because there is no basis for Canada's theory.

4.153 Third, during the proceeding we have heard a lot about the risks of an "endless loop of litigation" by a "mere declaration of compliance". Yet, as everybody agrees that the EC has adopted its compliance measure in good faith, it is clear that this "endless loop of litigation" does not arise in this dispute. Indeed, such an endless loop scenario presupposes a sort of scam measures notified by a WTO Member in bad faith. This is not the case before us. Indeed, even the EC would not consider that a "mere declaration of compliance" is sufficient but what matters is that a Member complies with its obligations. This is what the EC had actually done in this case after a most thorough review of its measure involving a comprehensive review and assessment of the available scientific evidence.

4.154 There is a paradox about the approach of the defendants to the principle of good faith. They do not contest that the EC has acted in good faith but they argue that WTO Members in general cannot be expected to act in good faith. They argue, Members with a duty to implement will adopt sham or scam measures to escape retaliation, it is argued that implementing Members must have the burden of proving their compliance. The EC does not believe that WTO Members act in bad faith. No Member wants to lose WTO disputes – and to do so repeatedly and ignominiously. There would be a high political cost. Also, WTO Members are not excessively litigious and do not gaily engage in endless loops of litigation. This fear is unfounded. But if this argument about bad faith is allowed, it can also be used the other way around – to argue that the United States' and Canada's approach will lead to Members seeking and exploiting retaliation rights for improper purposes. Seeking redress of WTO violations must not be too difficult; and implementation and removal of retaliation must not be made subject to the often impossible task of proving a negative. Retaliation rights should not become a new means of advancing unilateralist agendas.

4.155 Fourth, when it comes to the DSB authorization, the United States and Canada argue that this may be revoked if the EC would launch a proceeding under the DSU, be it Article 21.5, 22.8 or Article 25 etc. However, both defending parties cannot explain how this would even result in revocation of the DSB authorization. Well, Canada argues that the DSB could probably eventually make a recommendation to itself to revoke the DSB authorization but there is absolutely no basis for this in the DSU. And I am not talking about the procedural implications which this could entail. For instance – according to Canada – in an Article 21.5 proceeding brought by the EC against itself the burden of proof would be partly on the EC for the implementation of the original DSB recommendations and ruling. On the other hand, Canada could bring in its "defence" (in which they would complain about the WTO consistency of the measure) new claims for which it would bear the burden of proof. And of course, Canada's theory cannot even address the question on how these new claims could be reconciled with the more limited Panel request.

4.156 Finally, let me once stress again that the EC is not seeking to avoid a proper examination of its compliance measures in the Hormones dispute. We would be delighted if the United States and Canada would initiate an Article 21.5 dispute tomorrow and would do all we can to facilitate and accelerate its conclusion. However the United States and Canada stubbornly refuse to take this logical – indeed appropriate – step. It is they who have sought to avoid having to confront the new EC measures and set out their objections to it in a manner in which the EC can properly respond. They have, it is true, started to set out – for the first time – their objections in their first written submissions. The EC does not understand why they did not want to do this in a proper Article 21.5 proceeding.

4.157 We hope that we have assisted the Panel in its important task and look forward to helping the Panel in any further way that we can in the coming weeks.

F. ORAL STATEMENT OF CANADA DURING THE FIRST SUBSTANTIVE MEETING

1. Introduction

4.158 The EC was found in *EC – Hormones* to be acting inconsistently with its WTO obligations. It was given fifteen months to comply, but failed to do so. As a result, the DSB authorized Canada to suspend concessions to the EC, on the basis of which Canada adopted in 1999 the *European Union Surtax Order*. The consistency of Canada's measure was not challenged for many years, as it was understood to be adopted on the authorization of the DSB that remained in effect and as a part of a dispute that remained under the surveillance of the DSB. The EC is now, however, challenging the consistency of that measure.

4.159 What has changed? Canada's measure does not suspend concessions at a level higher than originally authorized; there has been no mutually satisfactory solution; the DSB has not revoked its authorization; and there have been no findings of EC compliance. Rather, the EC claims that what has changed is that it has adopted Directive 2003/74/EC, amending the EC measure originally found WTO-inconsistent. The EC notified to the DSB that with these amendments it "considers itself" to have fully implemented the recommendations and rulings of the DSB in *EC – Hormones* dispute and therefore Canada's measure is no longer justified. The EC did not ask whether the DSB "considers" the EC to be in compliance, nor did it ask whether Canada and the United States "consider" the EC to be in compliance. It simply asserted that it "considers itself" to be in compliance. While the EC alleges Canadian "unilateralism", it is the EC that has engaged in unilateralism: it is the EC that has unilaterally determined that it now complies and that the DSB authorization no longer applies. On the basis of these unilateral determinations, the EC alleges that Canada's measure is WTO-inconsistent.

4.160 While the EC seeks to prevent the Panel from considering the issues in the context of *EC – Hormones*, for it to prevail on any of its allegations, the Panel initially will have to make findings that relate in some way to the issue of the EC's "compliance". In fact, all parties agree that this dispute turns on the current status of the EC measure under WTO law. For the EC, the issue is whether the EC is *presumed* to have complied; for others, the issue is whether the EC has *actually* complied.

4.161 Since the EC does not benefit from a presumption of compliance, Canada cannot be found to have acted inconsistently with its WTO obligations without considerably more evidence and argument from the EC on how it has actually complied. The EC acknowledges itself in its alternative argument that if the Panel finds that the EC does not benefit from a presumption of compliance, the only way for it to prevail on its allegations would be for it to demonstrate its actual compliance. However, the EC falls far short of meeting even the lowest threshold of evidence and argument required to discharge this burden. Despite the fact that it is not Canada's burden to do so, Canada will highlight some of the reasons why the EC has not complied with the recommendations and rulings in *EC – Hormones*.

2. Since the EC is not presumed to have complied, Canada has not acted inconsistently with its obligations under the DSU

4.162 The EC's claim that it should be presumed to have complied with the recommendations and rulings in *EC – Hormones* is unsustainable. Rather, the EC bears the burden of having the DSB authorization terminated by seeking multilateral confirmation of its actual compliance.

(a) The EC's measure does not benefit from a presumption of compliance

4.163 The EC's claims rely on the general principle that States are presumed to act in conformity with their international obligations. While not disagreeing with this principle, Canada does disagree that it applies in these circumstances. The presumption of compliance applies to WTO Members prior to them being engaged in a WTO dispute. It even applies to WTO Members found to be in breach, as long as they comply within the prescribed period, and prior to authorization to suspend concessions. If the EC measure had been adopted outside the context of a WTO dispute, or if it had been adopted within the period granted to the EC to comply once it was found non-compliant, it would have benefited from a presumption of compliance. But in this case, the EC has abused its privilege of being granted a period of time to comply. The resulting DSB authorization gave the original dispute an entirely different legal character, altering the "fundamental logic" that underpins the presumption of compliance. Since the WTO compliance of Canada's measure cannot co-exist with the presumed compliance of the EC's measure, the latter must yield to the former. The explicit authorization granted under the terms of the DSU must prevail over a presumption of compliance. Therefore, the EC cannot claim the benefits of such a presumption.

(b) The EC bears the burden of demonstrating that its has complied

4.164 According to the EC, the presumption that its measure complies simply "overtakes" the DSB authorization, automatically rendering Canada's measure non-compliant. However, it cannot be correct that a unilateral assertion of compliance is sufficient to terminate a multilateral authorization. The EC's unilateralist approach to terminating the authorization runs directly counter to the object and purpose of the dispute settlement system that disputes be decided multilaterally and in a manner that ensures the security and predictability of the trading system. Since the DSB authorization is based on findings that the EC was non-compliant, it is up to the DSB to revoke that authorization should it subsequently find that the EC has complied. The onus is now on the EC to take appropriate steps within the multilateral system to confirm its compliance if it wishes to have the DSB authorization terminated. No provision of the DSU prohibits the EC from either initiating proceedings under Article 21.5 of the DSU or initiating proceedings *de novo*.

(c) Canada has not acted inconsistently with Articles 22.8 and 3.7 of the DSU

4.165 The EC alleges that Canada has failed to terminate its suspension of concessions despite the EC's notification that it has "removed" the measure found to be inconsistent in *EC – Hormones*. Canada agrees that the issue is whether the EC has complied and Canada also agrees that its suspension of concessions may only be temporary, but this is where agreement ends. The EC justifies its claim that its measure has been "removed" on the basis that it is presumed to comply – a presumption that Canada has demonstrated does not apply in these circumstances – but the EC has neither sought nor received multilateral confirmation of this. In the absence of a presumption of compliance or multilateral confirmation of compliance, the EC has not satisfied the pre-conditions of Article 22.8 of the DSU, and Canada cannot therefore be held to have contravened that provision. Without a finding that Canada has contravened Article 22.8 of the DSU, Canada also cannot be found to have acted inconsistently with Article 3.7 of the DSU.

(d) Canada has not acted inconsistently with Articles 23.1, 23.2(a) and 21.5

4.166 The EC's claims that Canada is seeking the redress of a perceived WTO violation (Article 23.1 of the DSU), that Canada has made a unilateral determination regarding the consistency of the EC measure (Article 23.2(a) of the DSU) and that Canada's failure to initiate compliance proceedings constitutes prohibited unilateral conduct (Article 21.5 of the DSU) are also unsustainable. Contrary to the EC's mischaracterization of the legal basis for Canada's actions, Canada is not seeking the redress of a perceived WTO violation; Canada has already sought and obtained redress, after which it was authorized by the DSB to suspend concessions to the EC. Since it is this authorization – which remains in effect in the absence of confirmation of EC compliance – that continues to form the basis of Canada's suspension of concessions, Canada's assessment of the inconsistency of the EC's recent amendments is unrelated to, and irrelevant to, Canada's measure. Any interpretation of the DSU that would compel Canada to initiate proceedings to challenge the EC's measure runs counter to the principle that WTO Members cannot be compelled to launch proceedings.

3. The actual compliance of the EC's measure with the recommendations and rulings of the DSB

4.167 In the absence of a presumption of compliance, the EC must establish that it has actually complied with the recommendations and rulings in *EC – Hormones*. While the EC chose not to have an Article 21.5 panel confirm its compliance, if the EC wishes to see the DSB authorization cease to apply, it must have this Panel confirm its actual compliance, although it appears unenthusiastic to do so and has submitted insufficient evidence on this point. Despite the fact that the EC has failed to demonstrate that it has complied, Canada will demonstrate why it has not.

(a) The EC has not presented a prima facie case that its measure complies

4.168 While the EC implicitly acknowledges in its alternative argument that it might bear the burden of demonstrating that it actually complies, the evidence it has put before the Panel falls far short of what is required to make a prima facie case. A prima facie case must be based on "evidence and legal argument" in relation to each of the elements of the claim. While the EC claims that it has complied, it has put forward mere assertions of compliance. It does not attempt to substantiate these assertions in relation to the recommendations and rulings in *EC – Hormones*. For example, it has not provided any evidence, nor advanced any arguments, that the documents it claims to be that risk assessment relating to oestradiol-17β actually constitute a "risk assessment". Nor does it explain how it has met the requirements justifying its ban on the five other hormones as a provisional measure. The Panel should also reject the EC's alternative claims that its measure actually complies.

(b) The EC's measure does not comply

4.169 Canada will nonetheless demonstrate that, were the EC to make a more substantial attempt to establish the actual compliance of its continued hormones ban, it would be unable to do so.

(i) The permanent ban on oestradiol-17β

4.170 The EC fails to satisfy the two conditions required to demonstrate that its permanent ban on oestradiol-17β is based on a risk assessment: that the SCVPH opinions constitute a "risk assessment", and that the EC measure is "based on" that risk assessment. The SCVPH opinions do not identify adverse effects arising from oestradiol-17β when used specifically as a growth promotant, nor do they evaluate the potential that these effects will occur. Much of what has been presented is speculation – based on incomplete and unconfirmed science – about potential adverse effects of oestradiol-17β consumed via meat from treated animals.

4.171 The more conclusive the evidence is about potential adverse effects associated with oestradiol-17β in specific circumstances, the less applicable that evidence is in identifying and evaluating any adverse effects associated with oestradiol-17β consumed through meat from treated animals. The SCVPH concludes – without evidence – that concern about the adverse effects of oestradiol-17β in specific circumstances is relevant to the use of oestradiol-17β as a growth promotant. Since the quantity of oestradiol-17β absorbed by the human body from residues in meat is a fraction of that absorbed from other sources, the identification of adverse effects that may occur as a result of the latter does not automatically suggest that adverse effects may occur from the former. The SCVPH acknowledges that it has no evidence that the potential adverse effects it identifies arise from the consumption of meat from treated animals.

4.172 The SCVPH places considerable emphasis on oestradiol-17β as a possible genotoxin, presenting a profoundly problematic hypothesis about how reactive oestrogen metabolites can damage DNA and initiate tumours. This hypothesis has emerged from a limited set of studies done at exceedingly high doses either on laboratory animals or *in vitro*. The SCVPH has disregarded or downplayed – because it refutes its hypothesis – established scientific evidence that defence mechanisms exist to control the formation of potentially genotoxic metabolites. The SCVPH's incomplete model of genotoxicity has attracted little support from the international scientific and regulatory communities.

4.173 While reasonable and responsible governments may act on the basis of minority scientific opinions, these minority opinions must be based on credible evidence of actual adverse effects and not on hypotheses and speculation based on models that disregard established scientific principles. The SCVPH fails to address the issue of the dose required to create an adverse effect, but concludes anyway that no dose threshold level can be established. In other words, the SCVPH presents no evidence that an adverse effect that may theoretically occur at high levels of oestrogen metabolites actually does occur at normal levels of oestradiol-17β, nor does it present evidence that the residues in meat from treated animals are capable of reaching this theoretical level. Therefore, the three SCVPH opinions do not individually, or collectively, constitute a risk assessment.

4.174 With respect to the second condition – that the EC measure must be based on a risk assessment – since the opinions on which the EC relies do not amount to a risk assessment for the purposes of the *SPS Agreement*, the measure cannot be said to be "based on" a risk assessment.

(ii) The "provisional" ban on the other five hormones

4.175 As for the EC's "provisional" ban on the other five hormones, the EC appears to be availing itself of the qualified exemption provided for in Article 5.7 of the *SPS Agreement*. The EC bears the burden of proving that its "provisional" measure meets the four cumulative requirements. The EC must first demonstrate that its provisional ban was adopted in a situation where the "relevant scientific evidence is insufficient" to allow it to perform a risk assessment. Second, the EC must demonstrate that its provisional ban was adopted on the basis of "available pertinent information". Third, in order to maintain its provisional ban, the EC must seek to obtain the additional information necessary for a more objective assessment of risk. Fourth, it must review its ban accordingly within a reasonable period of time.

4.176 The EC has made no attempt to demonstrate the "insufficiency" of the scientific evidence relating to the five provisionally banned hormones. The body of scientific data relating to these five hormones is such that the EC cannot plausibly argue that there is "insufficient" scientific evidence to conduct an adequate risk assessment. Since the five hormones have been the subject of multiple scientific assessments by reputable national regulatory agencies and international expert committees such as the JECFA, the EC's contention that there is insufficient scientific evidence to do so is simply not credible.

4.177 The EC has also not established that there is a rational connection between its provisional ban and the "available pertinent information" on these five hormones, including information from relevant international bodies such as JECFA and Codex. In fact, the EC's hormones ban is inconsistent with JECFA's conclusions and with the standards adopted by Codex regarding residues of these hormones in meat.

4.178 Finally, the EC has presented no evidence that, while maintaining its hormones ban, it is fulfilling the third and fourth substantive requirements of Article 5.7 of the *SPS Agreement*. It has been nearly two years since the adoption of the EC's so-called provisional ban on these five hormones. Yet there is no indication that the EC has reviewed its measure in the light of the scientific data available in the intervening period leading to these proceedings.

4. Conclusion

4.179 In order to resolve this dispute, the first finding of the Panel in this case will have to relate to the current status of the EC measure under WTO law. The EC claims that it should be presumed to have complied with the recommendations and rulings of the DSB in *EC – Hormones*, and as a result Canada has acted inconsistently with several of its DSU obligations. However, without the benefit of a presumption of compliance, the EC cannot succeed on the basis of the arguments it has made so far. Canada's DSB authorization remains in effect, and it is the EC that bears the burden of proving that it now complies. If the EC continues to refuse to discharge its burden under the DSU to demonstrate its own compliance, the outcome of this case is decided. On the other hand, if the EC accepts that burden, Canada has provided some of its own views on whether the EC has actually complied. Seven years after the DSB issued its recommendations and rulings in *EC – Hormones*, the total ban re-issued by the EC remains unwarranted by the evidence adduced.

5. Concluding statement of Canada

4.180 As is typically the case at this stage of dispute settlement proceedings many points have been made by the participating parties on many subjects. You may not find all of the points raised to be necessary for the purpose of reaching a proper resolution. With this in mind Canada would like to reinforce some of the basic issues at stake that have been raised before you.

4.181 In 1998, the EC was found by the DSB in the *EC – Hormones* dispute to be acting inconsistently with its obligations under the *SPS Agreement*. In 1999, in an attempt to induce the EC to comply with its recommendations and rulings, the DSB authorized Canada to suspend concessions to the EC. Neither of these facts is contested. Pursuant to that authorization, Canada enacted the *European Union Surtax Order*, the measure now challenged by the EC. This is also not contested.

4.182 The EC adopted a Directive in 2003 that it considers to have implemented the recommendations and rulings of the DSB. The EC now claims that the moment that it notified the DSB that it had adopted this implementing measure, Canada was required either to remove its measure or to challenge the EC's measure. The EC claims that this is the case regardless of whether the DSB has confirmed its compliance.

4.183 How does it happen that Canada's measure enacted as a consequence of a multilateral authorization cannot be applied subsequent to the EC considering itself that it has brought itself into compliance and notifying the DSB to this effect?

4.184 Apparently the answer is that the EC is presumed to have complied such that its implementing measure prevails over Canada's duly-authorized measure. Moreover, not all measures of all Member States benefit from the same presumption. According to the EC, only those that satisfy some arbitrary criteria that have no textual basis in the terms of the DSU benefit from this presumption.

4.185 Despite the EC's efforts to make this dispute a case about presumptions, the key to resolving the dispute lies first in determining how, and at the initiation of which party, the actual compliance of the EC is to be confirmed multilaterally. In fact, all of Canada's actions at issue in this dispute can be explained – not in terms of Canada having made any determination about the compliance of the EC's amendments – but in terms of Canada requiring, in the absence of mutual agreement, multilateral confirmation that the EC has complied. The EC asserts that it has. Canada disagrees.

4.186 But the fact of the matter is that due to the existence of Canada's authorized suspension of concessions, neither the EC nor Canada on its own can make such a determination. The only determination of EC compliance that matters at this point is one that must be made by the DSB. And until that happens, Canada is under no obligation to remove its measure. The issue remains, however, as to how to have the DSB arrive at such a determination.

4.187 The EC would like to make this dispute about good faith. Canada does not question whether the EC is acting in good faith. For Canada, the issue is simply one of compliance, and more importantly, which party bears the burden of demonstrating the compliance of the measure taken by the EC to implement the recommendations and rulings of the DSB.

4.188 In our view, and as the EC itself readily admits, it is the party alleging the affirmative of a claim that bears the burden of proof. In this case, since it is the EC that is alleging that one of the three elements of Article 22.8 has been met, it bears the burden of proving it. The EC's claims notwithstanding, Article 22.8 is not "self-executing". To suggest that the EC needs simply to notify its "removal" in order for Canada to be required to remove its measure, is just another way for the EC to say that its unilateral declaration of compliance can terminate a multilateral authorization. Further, in this case it is the EC that is alleging that Canada's presumptively valid DSB authorized retaliation measure ceases to apply. The EC can only effect this by demonstrating the validity of its own measure.

4.189 With respect to DSU Article 23, this provision only applies where, subsequent to a WTO Member making a unilateral determination that another Member has violated a WTO obligation, the Member making the determination then seeks to redress that perceived violation by methods other than DSU dispute settlement. The question of unilateral determination in this case is a moot point. All WTO Members make their own assessments of the consistency of other Member's measures on a regular basis. What is relevant is whether a Member has acted on that assessment to seek redress outside of the dispute settlement process.

4.190 While the EC asserts that its violation that permitted the DSB to authorize Canada's measure no longer exists, it insists Canada must forego the exercise of that measure even where the EC declines to put the matter before a panel. Also, if we understand the EC correctly, even if Canada were to submit the matter to a panel, because of the presumed compliance of the EC's measure, Canada cannot apply its DSB authorized measure while that review takes place.

4.191 Is there a disagreement between Canada and the EC? The EC thinks its measure complies. As stated earlier, Canada disagrees. However, it doesn't follow that Canada is now obliged to initiate a panel under Article 21.5. In the past week the Panel has heard agreement that the DSU provisions we are dealing with contain many interpretative difficulties. Clearly the rules are not a model of clarity.

4.192 However, one thing is clear. Article 21.5 does not create an *obligation*. It creates a *right* that WTO Members can use in dispute settlement proceedings. Somehow, the EC reconstructs it as an obligation in conjunction with Article 23.

4.193 Canada is not advocating a formalistic approach to the termination of the DSB authorization. What we are saying is that Canada is entitled to rely on this DSB authorization until such time as the EC demonstrates to a WTO panel that the basis on which the DSB authorization was granted no longer exists. It is insufficient, as the EC has done in this case, to simply assert that the basis of the authorization no longer exists as a matter of fact. The EC must prove that this is so by demonstrating to this Panel that it has complied with the recommendations and rulings of the DSB. Until such time as the EC has met this burden, Canada's suspension of concessions remains authorized by the DSB.

G. SECOND WRITTEN SUBMISSION OF THE EUROPEAN COMMUNITIES

1. Introduction

4.194 The European Communities' case is straightforward. WTO Members that apply sanctions against another WTO Member cannot adopt a lean-back-and-wait-attitude over years and continue to suspend concessions in the presence of a subsequent compliance measure. Just as WTO Members who have been found to be in violation of the covered agreements have a positive obligation to implement, so have retaliating Members a positive obligation under Article 22.8 not to apply sanctions any more and/or, if they disagree with the compliance measure, to initiate WTO proceedings under Article 21.5 of the DSU. This has always been the practice in WTO proceedings. If a retaliating WTO Member fails to respect these rules and procedures under the DSU, it will be in violation of Articles 23.1 and 23.2(a) of the DSU.

2. PART 1: Violation of Articles 23.1, 23.2(a), 21.5 and 22.8 of the DSU (systemic issues)

(a) Canada is in violation of Article 23.1 and 23.2(a) read together with Article 21.5 of the DSU

4.195 The existence of a DSB authorization does not exclude that a WTO Member is still seeking to redress a violation within the meaning of Article 23.1 and making a determination under Article 23.2(a). The very fact of applying sanctions implies that a Member is seeking to redress a violation. And this in turn implies that this WTO Member has made a "determination" about the WTO-inconsistency of the measure. The application of these sanctions may be justified if a measure by a WTO-Member has been properly found to be WTO-inconsistent and, if on that basis, the DSB authorizes the suspension of concessions. However, the situation is different regarding the *continuation* of sanctions in the presence of a compliance measure which the DSB has not found to be WTO-inconsistent. A DSB authorization which has been granted in view of an original WTO-inconsistent measure can not justify the continued application of sanctions against a different measure which has never been found multilaterally to constitute a WTO-violation. Rather, since the application of sanctions requires a causal relationship to a WTO-inconsistent measure, any *present* application of sanctions must be linked to a *present* measure. Conversely, the *present* application of sanctions to a *past* and no longer existent measure is not justified as it would be unjustified to link the *present* application of sanctions to a *future*, not yet existing measure.

4.196 Canada's counter-argument would lead to the absurd result that Canada could continue to apply sanctions irrespective of any events occurring after the DSB authorization and thus ignoring the object and purpose of sanctions, i.e. to induce compliance and to rebalance rights and obligations in case of a WTO violation. If Canada applies sanctions merely because of the existence of a DSB authorization and irrespective of a subsequent compliance measure, it is neither inducing nor rebalancing anything.

4.197 The true motives for Canada's continued application of sanctions are revealed by Canada's reply to EC Question No.13. Canada makes a link of its current measure to the original purpose of the DSB authorization. Yet, as the original purpose of the DSB authorization was to induce compliance and to rebalance rights and obligations, Canada obviously determines that the EC compliance measure

has not achieved either and that, therefore, the original purpose still exists. By doing so, Canada acts in an illegal way because the continued application suspension of concessions is thus based solely on a unilateral determination of non-compliance. Canada's action also fits precisely into the definition of "seeking of redress" as developed by the relevant case law.

4.198 In this context, Canada has also met the threshold of a unilateral "determination" in violation of Article 23.2(a). The term "determination" is defined, *inter alia*, as an "authoritative opinion"; "a conclusion reached"; "the action of coming to a decision"; "the result of this"; "a fixed intention". This term has been further elaborated by the Panel in *US – Section 301 Trade Act*. Thus, even an implicit determination by the appropriate behaviour, such as the continuation of sanctions, would be covered by a "broad reading" of this requirement, in particular, if the continuation occurs deliberately and is accompanied by respective statements.

4.199 Moreover, the interpretation of the word "determination" should be guided by the context of Article 23.2(a), i.e. Article 23.1, and the object and purpose of this provision. This provision as a whole aims at preventing that a Member takes "the law in its hands" and seeks the redress of a violation on the basis of a unilateral determination. The importance of this general principle is confirmed by the title of this provision. The crucial importance of Article 23 has also been acknowledged by the Panel in *US – Section 301 Trade Act*. It is therefore necessary to look at a Member's behaviour as a whole when confronted with a respective situation. If a WTO Member repeatedly and consistently states that a violation by another Member exists and if, in this context, this Member applies concrete measures against the other Member, it can be concluded that this Member is seeking a redress against a violation on the basis of a unilateral determination. Applying these principles to the present case, there can be no doubt that Canada has made a unilateral "determination" of non-compliance of the EC measure. This is already demonstrated by Canada's comments in the SPS Committee in respect of the EC draft proposal as early as in 2000 as well as its comments in the DSB meeting of 1 December 2003.[18] Considering Canada's whole conduct there can equally be no doubt that Canada has made a "determination" since it deliberately *continues* to apply sanctions against the European Communities.

4.200 By refusing to initiate a compliance proceeding in this situation, the European Communities considers that Canada is also in breach of Article 21.5. Canada's counter-argument that such an obligation would "vitiate" the existence of the DSB authorization is fallacious as Canada is essentially saying that it cannot be obliged to invalidate its DSB authorization by initiating and losing an Article 21.5 proceeding. The European Communities does not believe that this is the correct reading of the DSU. Apart from policy reflections Canada has not offered any legal arguments on why the continued application of sanctions is not violating Article 21.5 in conjunction with Articles 23.1 and 23.2(a). Canada fails to understand that in this case the obligation to initiate a compliance review under Article 21.5 is linked to its continued application of sanctions against the EC compliance measure. Because of this continued application of sanctions against the European Communities, Canada is under a positive obligation to bring a compliance proceeding against the EC measure. Thus, in this specific situation, Canada's discretion regarding whether or not it is appropriate to initiate WTO proceedings is limited as the failure to do so automatically encroaches on the EC rights, i.e. its right not to be exposed to sanctions for a measure which another WTO Member unilaterally determines as WTO-inconsistent.

4.201 Canada's argument that an obligation to initiate a compliance proceeding in this specific situation would "seriously undermine" the WTO dispute settlement system is for these reasons equally not credible. The purpose of the WTO dispute settlement system is not the application of sanctions but to resolve disputes in a prompt manner. Canada's protracted application of sanctions and its refusal to initiate a compliance proceeding against the EC measure runs diametrically against this very basic

[18] WT/DSB/M/159.

objective of the WTO. The WTO dispute settlement system has to balance the interests of complaining and defending parties, it is not an exclusive tool for a retaliating Member. Consequently, a Member in violation of its WTO obligations is under an active obligation to comply. Conversely, the retaliating Member is under an active obligation to initiate a compliance review under Article 21.5 and failure to do so will result in a violation of Article 23.1, 23.2(a), 21.5 of the DSU.

4.202 Finally, the European Communities would take issue with Canada's theory regarding a self-initiated Article 21.5. As repeatedly stated in its Written and Oral Statement, it is not possible or meaningful to initiate a compliance review against its own implementing measure. The DSU is based on a contradictory proceeding whereby a complaining party alleges a WTO-violation against another party. Conversely, the DSU does not provide for a situation where a "complaining party" alleges the WTO-consistency of its own measure, in particular to prove the negative that its measure is *not* WTO-inconsistent. Contrary to what Canada asserts this is also clearly spelt out in Article 6. The terms "complaining party" and "complaint" cannot be read in the "broad sense" as Canada suggests. The *New Shorter Oxford Dictionary* defines the term "complaint" as a "formal accusation or charge, a subject or ground of dissatisfaction". Obviously a case initiated under Article 21.5 would not fulfil any of these definitions as the European Communities would not bring a "charge" against its measure or express any dissatisfaction about its compliance measure. By way of context, Articles 3.8 and 1.1 also demonstrate the proper distribution of the parties' roles under the DSU.

(b) Canada's continued suspension of concessions and related obligations is in violation of Article 23.1, read together with Articles 22.8 and 3.7 of the DSU

4.203 The European Communities disagrees with Canada's assertion that the continued application of the sanctions is unrelated to the EC compliance measure. Since the original EC measure has been removed, Canada's argument would mean that Canada is currently applying sanctions against a non-existent measure. Such a conclusion would not only be illogical but also in plain contradiction with the very purpose of sanctions, namely to rebalance rights and obligations and to induce compliance in the light of a *current* WTO violation. Instead, as explained several times, it is obvious that Canada continues to apply sanctions because it considers the EC compliance measure as WTO-inconsistent. However, the continued application of an "old" DSB authorization cannot be justified against a "new" measure on which the DSB authorization is not based and if this measure has never properly been found WTO-inconsistent.

4.204 Contrary to what Canada believes the prohibition to continue the application of sanctions under Article 22.8 of the DSU does not depend on whether the DSB authorization has formally been removed. Article 22.8 of the DSU is unequivocal in the sense that the suspension of concessions and related obligations may only be "applied" until the inconsistency of the measure has been removed. Canada constantly fails to acknowledge the difference between the "existence" of a DSB authorization and the "application" of sanctions. Under Article 22.8 it is quite noteworthy that the scope of application of sanctions is limited to a "measure found to be inconsistent with a covered agreement". Yet, the only way to "find" a measure to be WTO-inconsistent under the DSU is through the multilateral procedure. Consequently, it is not possible to apply sanctions under Articles 22.8, 23.1 solely on the basis of a "unilateral finding" of inconsistency. In the same vein, the continuation of sanctions cannot be based on a unilateral finding of inconsistency of the compliance measure. In this context, the self-executing nature of Article 22.8 also needs to be taken into account. The termination of the application of sanctions under this provision does not depend on a specific finding of the DSB or a withdrawal of the DSB authorization. Rather, once the conditions under Article 22.8 of the DSU are met – including in the presence of an unchallenged compliance measure – the application of suspension "shall" stop.

4.205 The European Communities also takes issue with Canada's assertion about the reversed burden of proof in this "post-suspension scenario". Apart from the fact that Canada's theory is rooted

in the misconception that otherwise the DSB authorization would be terminated merely on the basis of a presumption of good faith compliance it has also no basis whatsoever either under WTO law or under public international law. The WTO jurisprudence is crystal clear that the party bearing the burden of proof is the one that asserts the *affirmative* of a claim or defence. Furthermore, the burden of proof is one concrete example of the general good faith principle, i.e. the presumption of compliance. This principle applies to an implementing measure as such but not to a specific timing when the measure had been adopted. The absurdity of Canada's theory is best exemplified in the present case where the European Communities had to study in detail the difficult scientific questions. Because of its carefulness the European Communities was not in a position to respect the reasonable period of time (RPT). Yet, according to Canada, if the European Communities had hastily adopted a compliance measure within the RPT this measure would benefit from a presumption of compliance whereas a measure which has been prepared with much more carefulness does not.

4.206 Even though there might be a question about the relationship between this principle and the "application" of a DSB authorization, the DSU also provides for a solution to this question which is the compliance proceeding under Article 21.5. Thus, if a retaliating Member contests the WTO consistency of an implementing measure it must initiate a compliance proceeding. In this context, Canada's argument to the security and predictability of the trading system is also off the point. In Canada's view the only secure and predictable way of the trading system is obviously the application of sanctions. However, the application of sanctions under the DSU is not an objective in itself. The application of sanctions is designed to achieve full compliance with the WTO obligations by another Member. Thus, if a violating Member has adopted compliance measures in good faith, it is indeed a matter of security and predictability of the trading system that the application of sanctions ceases to apply, if these measures are never properly challenged.

4.207 Finally, the European Communities disagrees with Canada's theory regarding the way a DSB authorization may be terminated which is not supported by the text of the DSU. As explained in detail in the EC second written submission, Canada's theory contains a number of inconsistencies such as that it is the DSB that recommends to itself the termination of the authorization or perhaps the panel that recommends to the DSB to do so (contrary to Article 19) or in respect of an implicit revocation of the authorization through the adoption of reports. Yet, one wonders how such a recommendation could be made given that under Canada's theory, the DSB authorization makes the continued sanctions *by definition* legal. Also, this raises the question how the suggested implicit authority can be squared with Article 2.1 which explicitly lists the tasks of the DSB. An implicit revocation of a DSB authorization is not included in this list. In the same vein, Article 2.4 refers to the decision-making powers of the DSB "where the rules and procedures of this Understanding provide". Yet, Canada cannot explain where the DSU provides for such an implicit revocation of a DSB authorization. Furthermore, under Canada's theory new "claims" would suddenly become "defences" even in case of a self-initiated Article 21.5 proceeding. This means in other words that Canada assumes a right to redraft the Panel's terms of reference on the basis that a new claim (e.g. a violation of Article III) is a "defence" against an old claim (e.g. Article I). However, Canada cannot explain how an alleged violation of Article I could be "defended" by a new violation under Article III. Moreover, Canada appears to arguing the absurd theory that the subject-matter of an Article 21.5 is not only the compliance measure but also the application of the sanctions which is however, in plain contradiction to the terms of Article 21.5.

3. PART 2: The WTO-consistency of the EC compliance measure

4.208 The European Communities, in its Oral Statement at the first substantive hearing as well as in a number of replies to the Panel's questions, has explained the various steps undertaken to carry out the comprehensive risk assessment which led to the adoption of its implementation measure, i.e. the revised Hormones Directive 2003/74/EC. As the Appellate Body found that the studies and other evidence presented by the European Communities was relevant but not sufficiently specific, the

objective of the compliance effort undertaken was to re-assess all existing and most recent data from any relevant source for the six hormones and to complement these data in particular in three respects, namely: (a) on certain issues regarding specific health risks from residues in meat treated with hormones for growth promotion purposes, (b) on risks arising from possible abusive use and difficulties of control, and (c) on an appropriate risk assessment for melengestrol acetate (MGA), which had not been carried out so far. To this effect the European Communities launched 17 specific studies and tried to collect information from all relevant sources, including from third countries, international scientific bodies (such as JECFA) and industry. All these steps were undertaken in full transparency and after consulting the relevant scientific committees and bodies that are responsible under Community law to conduct this kind of assessment.

4.209 In November 1998, the European Communities mandated its Scientific Committee on Veterinary measures relating to Public Health (SCVPH), to address the potential risks to human health from hormone residues in bovine meat and meat products treated with the six hormones for growth promotion. The SCVPH adopted its opinion unanimously taking into account all pertinent scientific information available at the time, including JECFA's revised assessment of the three natural hormones oestradiol-17β, testosterone and progesterone that had been issued in February 1999. The 1999 Opinion concluded that a risk to the consumer had been identified with different levels of conclusive evidence for the six hormones evaluated. Subsequently, the SCVPH was twice requested to review its opinion in light of new assessments carried out by other bodies or institutions and new evidence. The SCVPH did so in 2000 and 2002. The SCVPH concluded both times that the new evidence did not provide convincing data and arguments demanding revision of its previous conclusions. On the basis of the above scientific risk assessments provided by the SCVPH, the competent European regulatory authorities carried out an analysis of risk management options in light of the appropriate level of protection it had chosen. This lead to the adoption of the EC' compliance measure 2003/74/EC.

4.210 As explained in detail in the second written submission, JECFA's assessment proved insufficient in various respects and where the SCVPH conducted a more thorough analysis. These areas concern *carcinogenicity* of the three natural hormones and the outdated *residues data* as well as for data concerning the dose-response relationship. In respect of the latter, JECFA also neglected the endogenous production in the case of *pre-pubertal children.* Furthermore, the 1999 JECFA report has been seriously undermined by recent developments concerning the *bioavailability* of residues of these hormones. JECFA also failed to address the possibilities for *misuse or abuse* when the administration of these hormones is freely authorized "over the counter", as is the situation in the United States.

4.211 Turning to the legal arguments, the European Communities disagrees with Canada's arguments regarding the burden of proof. The European Communities, at the oral hearing and in reply to the Panel's questions, has demonstrated a violation of Articles I:1 and II of the GATT 1994 by Canada and that the measure found to be inconsistent has been "removed" in the context of a direct claim under Article 22.8. In particular, the European Communities has pointed out that it cannot be required to prove a negative, namely that there is no violation of WTO obligations. In line with the established case law of the Appellate Body, it is for Canada, in this case, to set out a prima facie case of violation, and not for the European Communities to set out a case of non-violation.

(i) The ban on oestradiol-17β is in conformity with Article 5.1

4.212 The European Communities conducted a proper risk assessment within the meaning of Article 5.1 and Annex A Point 4 of the *SPS Agreement*. The European Communities has pointed out in its reply to Question 24 of the Panel, that there is a difference between a scientific risk assessment in the narrow sense clearly referred to here by Canada and the risk assessment within the meaning of Article 5.1 and Annex A Point 4 of the *SPS Agreement*. The latter, as has been stated by the Appellate Body, also comprises a risk management stage which is the responsibility of the regulator to carry out and not the scientific bodies. Canada concentrates its arguments on the alleged flaws in

the scientific risk assessment of the SCVPH and the European Communities will reply to these arguments.

4.213 Canada submits a series of factually and legally incorrect arguments in respect of the identification of the adverse effects. In particular, as the European Communities' written and oral submissions have shown, Canada's arguments are based on outdated data of its own or of JECFA and misinterpret the findings of the latest scientific evidence, including that generated by the 17 EC studies. Indeed, all the references in Canada's submissions are confined essentially to the findings of JECFA of 1988 and 1999 for the three natural hormones and of 2000 for melengestrol acetate. However, these findings by JECFA did not take into account the more recent evidence on which the 1999-2002 evaluations by the SCVPH are based. To overcome this obvious difficulty, Canada argues that the findings of the SCVPH are not specific to residues in meat. This argument of Canada is flawed, because the 1999 and 2002 Opinions of the SCVPH have a specific chapter for each of the six hormones about the dose-response question and the potential risks from residues in meat from animals treated with these hormones for growth promotion. Canada ignores the fact that even JECFA has declared oestradiol-17β for the first time in 1999 to have "genotoxic potential", which means that there is normally no safe threshold for any amount of residues in meat from this hormone. So the issue of specificity for this hormone becomes irrelevant. Canada's claims are also contradicted by the most recent evidence (the US for the first time in 2002 recognised in its National list of carcinogen oestradiol to be a proven carcinogen), which indicates that there is no safe threshold for this hormone. The SCVPH finding is also confirmed by more recent literature as well as more recent data of endogenous production by pre-pubertal children.

4.214 Canada's statement that the SCVPH Opinions did not clearly identify the presence of adverse effects is also incorrect as demonstrated by pages 41 to 43 and 72 of the 1999 Opinion. It is also incorrect, as demonstrated by the JECFA report, to allege that the SCVPH opinion based its conclusions on the genotoxic effects of oestradiol-17β on a hypothesis that is not recognized elsewhere. The UK Sub-Group Report also acknowledges the risk of genotoxic effects of oestradiol-17β. Finally, it is true that some foods that are part of a balanced human diet naturally contain oestradiol-17β. However endocrine hormones regulate a variety of physiological functions and their balance is a very delicate matter; in particular pre-pubertal children are the group of greatest concern in this respect. It is therefore necessary to reduce the amount of additional hormones the population is exposed to to a level that is as low as reasonably achievable by avoiding excess intake due to the use of hormones as growth promoters. It is necessary that substances used in animals provide reasonable certainty of no harm in particular if their use does not provide any benefit for the animals treated that would justify the tolerance of such harm. Therefore, if oestradiol-17β increases, e.g. the incidence of breast cancer as more recent studies seem to indicate, any avoidable increase, however small, is not desirable.

4.215 Contrary to what Canada asserts the risk assessment did also evaluate the potential occurrence of the adverse effects it purports to identify. This issue is referred to in the SCVPH Opinions in several points as specified in the EC second written submission. Furthermore, in arguing that the ban on oestradiol-17β is not based on a risk assessment, Canada essentially repeats the argument on the lack of specificity of the risk assessment which is, as explained, not of any value.

(ii) The provisional bans on five of the hormonal substances do not violate Article 5.7

4.216 Contrary to what Canada argues the provisional bans on the five hormonal substances progesterone, testosterone, trenbolone, zeranol and MGA are in conformity with Article 5.7 of the *SPS Agreement* because the current evidence is insufficient. The European Communities recalls that: (1) what the European Communities had considered to be sufficient evidence had been found to be insufficient by the Appellate Body and proved indeed to be insufficient also in the light of risk assessment standards that were developed in the years after the *EC – Hormones* decision; and (2) the

body of evidence, in the meantime, has developed and, while still not providing enough knowledge to carry out a complete and definitive risk assessment, supports the conclusion that precautionary measures are required in order to achieve its chosen level of protection.

4.217 As further detailed in its Written and Oral Submissions, the European Communities considers, on the basis of the 1999 – 2002 SCVPH opinions, that the current evidence is full of gaps in pertinent information and important contradictions that render the conclusions reached by JECFA in 1988, 1999 and 2000 no longer valid. Thus, it does not allow in qualitative or quantitative terms, the performance of an adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*. Furthermore, since the latest risk assessment by the SCVPH in 2002, there appeared internationally a number of further scientific developments all of which converge toward, and provide further support to, the conclusions reached by the relevant scientific committee of the European Communities, such as a study supported by the Ohio State University, the US National Cancer Institute and the US Department of Defence Breast Cancer Research program concerning zeranol (and oestradiol-17β) or a large scale epidemiological study in Europe suggesting that high red meat intake is associated with (statistically significant) increased colorectal cancer risk, confirming results from previous smaller studies. Additionally, in 2002, the women's health Initiative Randomised Controlled Trial published findings indicating that the risks outweigh the benefits from the use of oestrogen plus progestin in healthy postmenopausal women, thus reinforcing the previous findings made by the IARC in this respect. All this evidence and most recent scientific developments have now clearly tipped the balance against the previously held assumption (by Canada and Codex/JECFA) that residues of these hormones in meat from animals treated for growth promotion pose no risk to human health.

4.218 Consequently, the evidence which served as the basis in the 1988 and 1999-2000 JECFA evaluations of these hormones is not sufficient to perform a definitive risk assessment, in particular by the WTO Members applying a high level of health protection of no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion. To deny the existence of this new scientific reality would deprive the European Communities and other WTO Members of their autonomous right to choose their appropriate level of protection, because it would in effect impose on them a requirement to demonstrate positively the existence of clear harm, which they may not always be able to fulfil in case of cancer because of the long latency period and the numerous confounding factor that play a role. This will render the application of Article 5.7 impossible in a situation where the body of the pertinent scientific evidence is in the process of moving from a state of presumed "sufficiency" into a state of pertinent "insufficiency". The text and preparatory history of the *SPS Agreement* do not support such a (restrictive) construction of Article 5.7, which would moreover be against the principle of effective treaty interpretation.

4.219 Finally, Canada has not put forward any specific arguments as to why the available pertinent information on the five hormonal substances in question would not be insufficient, but instead sufficient. It has therefore failed to meet the burden of setting out any prima facie claim.

4.220 In any case, in its second written submission the European Communities has set out in detail the state of insufficient evidence as determined by the SCVPH for each of the hormones which have been provisionally (progesterone, testosterone, trenbolone, zeranol, MGA) prohibited by the Directive 2003/74/EC. In particular, as regards zeranol, Canada does not put forward any specific argument as to why the evidence assessed by the SCVHP would not be insufficient. The only assessment on zeranol publicly available is that of JECFA which dates back to 1988. The SCVPH took into account this assessment but disagreed with a number of its basic findings on the bases of more recent scientific evidence, some of which was generated by the 17 EC studies. Moreover, the most recent study on zeranol and the risks associated with its administration to meat producing animals is done by independent US scientists mentioned above and it clearly invalidates the findings of the 1988 JECFA opinion.

4.221 Furthermore, as regards MGA, there is currently no international standard or recommendation on MGA, as Codex has not adopted one. JECFA assessed MGA for the first time in 2000 (and in 2004 as regards the calculation of the MRL only), but this has not yet led to the adoption of a standard. If one examines the evidence that served as the basis of the 2000 JECFA report it can be seen that nearly all the studies referred to therein date from the 1960s and 1970s. These very old studies constitute in fact the evidence which the defending parties have refused to provide to the European Communities, despite its repeated requests on the grounds that they are confidential. In the absence of a Codex standard, the opinion of JECFA becomes irrelevant, for the additional reason that it failed to take into account the more recent data generated by the 17 EC studies and the 2002 SCVPH assessment. Canada does not put forward any specific argument as to why the evidence assessed by the SCVPH would not be insufficient. It does not even refer, in this context, to the fact that MGA, in the meantime (2000), has been assessed (for the first time) by the JECFA and which subsequently has been taken into account by the SCVPH in its 2002 Opinion.

4.222 The European Communities adopted the provisional prohibitions on the basis of the available pertinent information. The only argument that Canada raises in this regard is that the European Communities' measure is not based on JECFA's assessment. However, as the European Communities explained, JECFA's assessment was considered to be insufficient, because, *inter alia*, it was found to be outdated.

4.223 The European Communities has also not violated its obligation to seek to obtain the additional information necessary for a more objective assessment of risk or to review the measure in question. Canada does not put forward any convincing argument as to why the European Communities would have failed to fulfil its obligation to seek additional information. Indeed, the European Communities has specifically laid down that obligation in Directive 2003/74/EC. As a matter of fact, it has already undertaken initiatives to seek additional information. In particular, it has issued a new call for scientific data and research from 2002 onwards, on substances with hormonal activity which may be used for growth promotion purposes in bovine meat.

4.224 In the view of the European Communities, and as explained in reply to the Panel's Question 71, a requirement to review a measure "within a reasonable period of time" can only apply as of the coming into effect of the provisional measure in question. The Directive has come into effect on 14 October 2003. Thus, it can hardly be argued that a reasonable period of time has actually already elapsed.

4.225 The European Communities has moreover pointed out that Directive 2003/74/EC contains an obligation to "keep the measures applied under regular review with a view to timely presentation … of any necessary proposals." Regular review certainly implies reacting, as appropriate, to new evidence or information that may appear. As a matter of fact, the only new information that has come to the knowledge of the European Communities is the recent draft assessment of the UK Group. That draft report has already been forwarded to European Food Safety Authority for review. Equally, should the recent call for new scientific information (see above) yield any new evidence, such evidence would also be assessed by EFSA without any undue delay.

4.226 In conclusion, Canada has not put forward any convincing arguments to support its claim that the European Communities has violated Article 5.7 of the *SPS Agreement* in adopting a provisional ban on the five hormonal substances progesterone, testosterone, zeranol, trenbolone and MGA.

H. SECOND WRITTEN SUBMISSION OF CANADA

1. Introduction

4.227 Canada will demonstrate again that the EC's allegations under the DSU are without merit. The EC has recognized that the real object of these proceedings is to review the compliance of the EC measure with the recommendations and rulings of the DSB in *EC – Hormones*. Canada will elaborate further on that issue in this rebuttal submission.

2. The EC's claim under the DSU

(a) Canada has not acted inconsistently with Article 23.1 of the DSU

4.228 The EC claims that DSU Article 23.1 read "in conjunction with" Articles 23.2(a) and 21.5 imposes a new obligation on Canada that finds no textual basis, in that DSU Article 21.5 does not contain an obligation for any WTO Member to initiate compliance proceedings. The EC also claims that Article 23.1 "in conjunction with" DSU Articles 22.8 and 3.7 removes Canada's right to act in accordance with the DSB authorization to suspend concessions without multilateral intervention by the DSB (contrary to DSU Articles 3.2 and 19.2). This interpretation of DSU Article 22.8 would render WTO inconsistent, without multilateral confirmation of the EC's compliance, a Canadian measure enacted pursuant to a multilateral authorization.

4.229 Canada's continued application of an authorized measure suspending concessions cannot be a conduct inconsistent with Article 23 of the DSU simply because the EC claims it has complied. The EC's adoption and subsequent notification to the DSB of its purported implementing measure does not change the legal basis for Canada's measure. Given that the EC is responsible for obtaining multilateral confirmation that it has complied, Canada's conduct is not "seeking redress". The term 'redress' implies a reaction by a Member against another Member, because of a perceived WTO violation, with a view to remedying the situation. Canada's conduct is not aimed at remedying any perceived violations by the EC, but is based on the DSB authorization.

(b) Canada has not acted inconsistently with Article 23.2(a) of the DSU

4.230 Given that Canada is not "seeking redress", Canada cannot have made a "determination" within the meaning of Article 23.2(a) of the DSU. That provision applies only where a Member is seeking redress of a WTO violation. The panel in *US – Section 301 Trade Act* is the authority for this.

(c) Canada has not acted inconsistently with Article 22.8 of the DSU

4.231 Where concessions have been suspended on the basis of an authorization by the DSB (and absent a mutually satisfactory solution), the onus is on the Member originally found to be non-compliant to take steps to confirm multilaterally that it has satisfied at least one of the conditions of Article 22.8. Without such multilateral confirmation, the DSB authorization remains in effect and continues to authorize the suspension of concessions by the original complaining Member. The EC objects to this interpretation of its obligations on several unsustainable grounds.

(i) The EC must confirm its compliance in EC – Hormones

4.232 The result of the EC's failure to comply within the reasonable period of time is that it bears the burden of demonstrating that it has now complied with the recommendations and rulings of the DSB in *EC – Hormones* if it wishes to have the suspension of concessions no longer applied. Given that the 2003 Directive simply amends the 1996 Directive, a review of the compliance of this measure is not an abstract exercise about a review of the EC's compliance in this context. The DSB

authorization does not provide "absolute justification" for any behaviour. Rather, until the EC receives multilateral confirmation that it has brought itself into compliance, Canada is entitled to continue to rely upon the authorization. The immediate threshold issue is therefore which party bears the burden of confirming the compliance. The requirement that the EC bear this burden if it wishes to have the suspension of concessions ended is simply the logical consequence of the position in which the EC has placed itself in the *EC – Hormones* dispute.

(ii) Article 22.8 of the DSU is not "self-executing"

4.233 DSU Article 22.8 cannot be "self-executing" in the light of the overall DSU regime of surveillance in circumstances of non-compliance. In the light of the object and purpose of the DSU, and in the context of the other provisions relating to non-compliance, Article 22.8 requires multilateral confirmation that the conditions precedent have been satisfied before the suspension of concessions can no longer be applied. The authorization to suspend concessions as a result of a failure to comply is granted solely by the DSB. A subsequent, unconfirmed claim that Article 22.8 has been met is insufficient on its own to displace the multilaterally-agreed surveillance regime, regardless of how much effort is put into the measure underlying the claim.

4.234 The EC confuses several distinct issues related to "good faith" and "bad faith". The suggestion by the EC that denying the presumption of compliance would be tantamount to a finding of bad faith should be rejected. The issue of a presumption against bad faith is an entirely separate matter from that of compliance. A finding that a Member does not comply with its WTO obligations amounts to neither an accusation nor a finding of bad faith. According to the EC, the alleged self-executing nature of Article 22.8 is based on the degree to which its efforts to comply are serious and in good faith. Presumably, those who do not satisfy the criteria put forward by the EC bear the burden of demonstrating compliance, whereas those who do satisfy these criteria do not. However, the EC is silent on the mechanisms to determine whether a Member satisfies these criteria. It is to avoid this kind of subjective application of "criteria" that multilateral confirmation is required to give effect to Article 22.8.

4.235 The adoption of a measure in one Member cannot be allowed automatically to render WTO inconsistent a measure of another Member, without some intervening international act. In the light of the overall regime of compliance, the dispute settlement system requires actual findings of compliance or non-compliance before Article 22.8 can be given effect. That the EC bears this burden is the consequence of the status of non-compliance in which it has placed itself.

(iii) The DSB authorization need not be formally terminated

4.236 The obligation to remove the suspension of concessions does not only arise with the formal revocation of the authorization by the DSB. The more important substantive act (between the EC's claim of compliance and the acquisition by Canada of an obligation to remove the suspension of concessions) is "multilateral confirmation" that the EC measure found to be inconsistent in *EC – Hormones* is no longer inconsistent. While no specific provision in the DSU requires the formal revocation of the authorization, this does not mean that there cannot be an act by the DSB that is equivalent to revoking the authorization, whether that is implicit or explicit. The "multilateral confirmation" of compliance would generally come in the form of adoption by the DSB of panel findings of compliance. Thus "confirmation" of compliance and the "revocation" of the authorization are essentially the same act of the DSB.

(iv) The EC has several mechanisms to confirm compliance

4.237 The EC could have obtained multilateral confirmation of its compliance through DSU Article 21.5 proceedings. Nothing prevents the EC from initiating such proceedings. Nor, where

compliance is found, are there any limitations on the jurisdiction of such a panel preventing it from making recommendations to the effect that the DSB authorization should no longer apply.

4.238 The EC may also choose to confirm its compliance in proceedings *de novo*, such as in these proceedings, in order to have the DSB authorization terminated. The main objective of these proceedings should be a review of the compliance of the EC with the recommendations and rulings in *EC – Hormones*. The EC bears the initial burden of proof to demonstrate compliance.

3. The EC's compliance in *EC – Hormones*

4.239 In *EC – Hormones*, the EC measure was found inconsistent with the requirements of Articles 3.3 and 5.1 of the *SPS Agreement*. The EC now asserts that it has complied, on the basis that its permanent ban on oestradiol-17β is supported by a risk assessment within the meaning of Article 5.1 and that its provisional ban on the other five hormone growth promotants is justified under Article 5.7. It has failed to demonstrate this.

(a) The relevant international standards and the EC's level of protection

4.240 Pursuant to Article 3.3 of the *SPS Agreement*, the EC must demonstrate that there is "scientific justification" for its determination that international standards are "not capable of achieving [its] chosen high level of protection" of "zero additional risk". Whereas Codex established MRLs for TBA and zeranol, and decided that none was necessary for oestradiol-17β, testosterone and progesterone, the EC has determined that no threshold exposure levels can be established for any of the six hormones when administered for growth-promotion purposes. Since the SCVPH opinions fail to identify any "additional risks" from ingestion of residues of the six hormones at levels that comply with international standards, they fail to demonstrate that existing international standards are not capable of achieving the EC's appropriate level of protection. The EC measure is therefore also inconsistent with Article 3.3.

(b) "Risk management" under the *SPS Agreement*

4.241 The EC asserts that the risk assessment required by the *SPS Agreement* is "wider in scope" than risk assessment techniques developed by international organizations, that the latter is simply a scientific process, and that the former takes other factors into account at the "risk management" phase. The EC then submits that the three SCVPH opinions constitute a risk assessment only in the narrow sense, and argues that the "wider" risk assessment includes the process of weighing policy alternatives and selecting appropriate control options. This distinction between "risk management" and "risk assessment" is problematic for several reasons.

4.242 First, it finds no support in the *SPS Agreement* or WTO jurisprudence. The EC suggests that the Appellate Body findings in *EC – Hormones* mean that any element of what could be called "risk management" is part of a "wider" risk assessment. However, the findings cited only mean that certain factors cannot be excluded *a priori*. Based on its misreading of the findings, the EC makes the same error as the panel in *EC – Hormones*. Whereas the panel in that case erred in excluding certain factors from the risk assessment on the basis of its distinction, the EC now asks this Panel to include all factors in the risk assessment. This is an erroneous interpretation.

4.243 Second, the EC does not identify the "regulatory authority" responsible for "risk management", which policy alternatives it weighed and whether there is any documentation in support of this evaluation. It simply asserts that its authorities decided that hormones create an "avoidable risk". The EC has therefore not complied with the Panel's request for documentation and supporting information, suggesting instead that the mandate of the Panel is limited to reviewing the narrower,

scientific risk assessment. However, all components of the wider risk assessment should be subject to review.

4.244 Third, the EC inappropriately assimilates the appropriate level of protection, and the adoption of the SPS measure, directly into the risk assessment process. It includes "risk management" in the "wider" risk assessment and then includes in "risk management" the right to set the appropriate level of protection and implement appropriate control options. However, risk management cannot be both part of the risk assessment and part of the process of setting the appropriate level of protection and implementing control options. The EC's interpretation essentially renders meaningless the obligation that SPS measures be based on a risk assessment. The factors that can be considered in a risk assessment are clear, such as those listed in Article 5.2 and including non-scientific and non-quantitative analysis as well as evidence related to misuse. Those factors should be assessed here and not some undefined notion of risk management that finds no support in the *SPS Agreement*.

(c) The risk assessment and the EC's permanent ban on oestradiol-17β

4.245 The EC has failed to demonstrate sufficiently its claim that it has complied with *EC – Hormones* by basing its permanent ban on oestradiol-17β on a risk assessment.

(i) The SCVPH opinions do not amount to a risk assessment

4.246 The SCVPH opinions do not sufficiently complete the two-part analysis identified by the Appellate Body as the requirements of a risk assessment. Furthermore, they do not satisfy the requirement of Article 5.1 to take into account techniques developed by the relevant international organizations, which provide context and guidance to the Appellate Body's two-part test.

4.247 The EC qualifies this failure by arguing that risk assessments are "deterministic" and address poorly "non-linear" situations (presumably referring to genotoxicity). However, the fact that genotoxicity findings may change the approach taken in a risk assessment does not grant the EC licence to avoid completely its requirement, especially when those findings are speculative. Nor can it justify the deficiencies of the risk assessment with respect to other "linear" adverse effects. The EC argues that an exposure assessment is unnecessary when the data are unavailable, but its own scientific studies generated exposure data, finding that exposure to oestradiol-17β from meat from treated animals amounted at most to 16.6 percent of the ADI. In any event, other reputable scientific bodies have conducted complete risk assessments without encountering the limitations expressed by the EC.

4.248 The EC then claims the "table of contents" of the 1999 SCVPH opinion demonstrates that it is a risk assessment. Without any clear explanation by the EC, the table of contents is an unhelpful guide to understanding whether the SCVPH conducted a hazard characterization or a risk characterization. The EC points only to two excerpts that are summaries of the SCVPH's genotoxicity hypothesis and its speculation about the consequences. Neither excerpt amounts to a qualitative or quantitative evaluation of the nature of the adverse effects.

4.249 The SCVPH fails to conduct a dose-response assessment due to its conclusion that no threshold level can be established for genotoxic metabolites or for substances which might have other adverse effects. It provides no justification for its *a priori* rejection *of* the widely-accepted view that adverse effects arising from hormonal activity are dose-dependent. The EC defends the SCVPH on the basis that international risk assessment techniques only recommend such an assessment, but its obligation is to base its measure on a risk assessment that complies with the *SPS Agreement*. The EC refers to a reference in *EC – Hormones* to "qualitative assessment" to suggest that quantitative analysis is not required at any stage of its risk assessment. However, the Appellate Body found that a risk assessment need not identify a minimum, quantifiable magnitude of risk; it did not suggest that a

risk assessment could be conducted without any empirical evidence related to dose-response. An evaluation of the potential occurrence of adverse effects would seem nearly impossible without some idea of the dose of a substance required to provoke an adverse effect. A qualitative assessment is not simply a licence to substitute speculation and hypotheses for objective scientific analysis.

4.250 The SCVPH also failed to conduct an exposure assessment, yet the lack of data on residues in meat does not prevent it from drawing definitive conclusions about the risks arising from exposure to hormone residues from treated meat. The EC argues instead that its risk assessment was not required to conduct an exposure assessment in the light of the EC's decision to allow "zero additional risk". Since the EC has identified that hormones in general have adverse effects, and since consuming meat from treated animals presumably leads to higher intakes of hormone residues, consuming meat from treated animals must generate "additive risks", which according to the EC is all that is required. The EC does not demonstrate that hormone residues from meat from treated animals on their own create risks, nor does it identify the risks to which these hormones are said to be "additive".

(ii) The genotoxicity findings of the risk assessment

4.251 On the basis of the SCVPH's conclusion that oestradiol-17β is genotoxic, the EC rejects other international scientific bodies' findings, ignores current international standards, discounts traditional risk assessment techniques, characterizes hazards without assessing dose-response data, dismisses traditional scientific understanding about the bioavailability of oestradiol-17β, refuses to establish a dose-threshold level, and declares irrelevant the fact that growth promotants are used in low doses in animals. However, the SCVPH conclusion on the genotoxicity of oestradiol-17β is not supported by the evidence.

4.252 First, the SCVPH acknowledges that its conclusion that one single reactive metabolite of oestradiol-17β can damage DNA and lead to tumour initiation is simply a hypothesis. Its conclusion disregards established evidence that bodily mechanisms exist to control the formation of potentially genotoxic metabolites *in vivo* and to eliminate DNA adducts. Considering the SCVPH's acknowledgement that it has no "data on the genotoxic effects of exogenous low-dose oestrogens", its genotoxicity conclusion amounts to merely the identification of theoretical risk.

4.253 Second, other scientific and regulatory authorities have all indicated that the SCVPH's genotoxicity conclusion is more theory than reality. While acknowledging the "genotoxic potential" of oestradiol-17β, JECFA found this would not occur in vivo at physiological concentrations. The CVMP and the Veterinary Products Committee both concluded that there is no evidence that oestradiol-17β is genotoxic. In 2005, The Veterinary Products Committee agreed that oestradiol-17β may have genotoxic potential in theory, but found that there was a "threshold for carcinogenicity". The Australian Department of Health and Ageing found that even though oestradiol-17β may have genotoxic potential there is "no evidence that these occur *in vivo* at levels that would outstrip normal DNA repair mechanisms."

4.254 Third, the EC does not appear to believe that oestradiol-17β is genotoxic. Despite the EC's decision not to allow exposure to even one molecule of oestradiol-17β from meat from treated animals, it is strikingly silent on potential risks arising from all other sources of oestradiol-17β. The EC defence of zootechnical and therapeutic uses of oestradiol-17β is a response one would expect to dose-dependent adverse effects. The one single molecule from meat derived from treated animals that the EC considers so dangerous is suddenly not at all dangerous when consumed from meat from animals treated for other purposes. The risk of adverse effects from the genotoxicity of oestradiol-17β residues in meat from treated animals is more "theoretical uncertainty" than real-world risk. Theoretical uncertainty is not the kind of risk to be evaluated in a risk assessment, and the EC's genotoxicity conclusions cannot be used to warrant its measure.

(iii) The risk assessment is not "sufficiently specific"

4.255 The SCVPH opinions do not assess the specific risks associated with hormone residues in meat derived from treated animals, claiming that general evidence of hormone metabolites' genotoxicity renders specific evidence of residue genotoxicity unnecessary. Not only is there no convincing evidence of genotoxicity, but the specificity requirements in *EC – Hormones* cannot be so summarily disregarded. Even if the SCVPH's hypothesis is accepted, the SCVPH must confirm that a single reactive metabolite will actually result from low doses received from meat from treated animals. Instead, the EC's studies fail to find evidence of such metabolites.

4.256 The EC defends the SCVPH's failure to evaluate the dose of residues from meat from treated animals by stating that low dose is not relevant, and by asserting that the SCVPH did "take into account" the dose. However, it provides only the SCVPH's estimates of how much residue of oestradiol-17β will be consumed through animal tissues, without assessment of whether these residues create any specific risks. The SCVPH's assessment of hormone exposure from treated animals is therefore mere speculation about what these specific risks might be.

4.257 The EC further argues that it is necessary only "in principle" to assess the specific risk, that there are "important qualifications" to this obligation, that it cannot assess the specific risk due to the difficulty in estimating intake of residues from meat, and that it cannot estimate intake due to the variability of consumer exposure patterns and the lack of information about good veterinary practices. Not daunted by the absence of this evidence, the EC concludes by speculating that the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be.

(iv) Adverse effects from misuse and misplaced hormone implants

4.258 The EC disagrees with international standards, citing concerns about the difficulty in ensuring they are administered according to good veterinary practice. It has not provided a risk assessment evaluating the existence and level of risk arising from the potential for failure to comply with such practice. Instead, it refers to studies which purportedly formed the basis of the SCVPH's conclusions that implants are misused or misplaced "frequently" or "in daily routine", although such studies merely involve "experiments" addressing whether consumers would be exposed to higher doses of residues if hormone implants were misused. They address neither the actual occurrence of misuse, nor whether misuse would increase the potential occurrence of adverse effects. They also indicate that under misuse conditions, intake of hormone residues remains well below established ADIs. The EC only speculates that abuse leads to an increase in the potential occurrence of adverse effects. A risk assessment cannot be based on speculation about theoretical risks, but must address risks in the real world.

(d) The provisional ban is inconsistent with Article 5.7 of the *SPS Agreement*

(i) Article 5.7 is not a "special regime"

4.259 The EC's claim that Article 5.7 is a "special regime in relation to Article 5.1 of the *SPS Agreement* " and that it is for the party alleging a violation of Article 5.7 to make a prima facie case of non-compliance is without merit. The Appellate Body has found that the party that wishes to rely on the exception of Article 5.7 has the burden of showing that it has met its conditions.

4.260 Article 5.1 is a specific application of the basic obligation contained in Article 2.2 of the *SPS Agreement* not to maintain SPS measures without sufficient scientific evidence. A WTO Member adopting an SPS measure that results in a higher level of protection than would be achieved through a measure based on the relevant international standards must satisfy the requirements of

Article 5.1. Where a measure is not based on a risk assessment, a Member may justify its measure under Article 5.7 of the *SPS Agreement* on the basis that insufficient scientific evidence exists to perform an adequate risk assessment.

4.261 The recommendations and rulings of the DSB require that the EC base its measure on a risk assessment in accordance with the requirements of Article 5.1 of the *SPS Agreement*. The EC cannot circumvent this obligation by characterizing its measure with regard to five of the hormones at issue as "provisional" and then claiming that this "provisional" measure is subject, not to Article 5.1, but to the "special regime" of Article 5.7, which is "not covered by the rulings and recommendations of the DSB". Given that the EC has invoked Article 5.7 to justify its non-compliance with Article 5.1, it must bear the burden of demonstrating that the requirements of Article 5.7 have been fulfilled.

(ii) The relevant scientific evidence

4.262 The four requirements of Article 5.7 are cumulative in nature. The first one functions as a threshold requirement because Members may only adopt provisional measures "[i]n cases where relevant scientific evidence is insufficient".

4.263 To date, none of the reasons given by the EC explains in a convincing manner why the relevant scientific evidence is "insufficient" to allow the performance of an adequate assessment of risk. The EC takes issue with the risk assessments conducted by JECFA on the safety of the five hormones when used according to good veterinary practices because it alleges that it could not review the "basic information and raw data" underlying JECFA's conclusions. However, the majority of these data is in the public domain. Although the EC complains that Canada did not provide it with the scientific studies and data underlying its decision to authorize the use of these five hormones, Canada provided the EC with the full names and addresses of each of the firms with proprietary rights to the information the EC had requested. To date, the EC has provided no confirmation that it has contacted these firms.

4.264 The EC also takes issue with JECFA's conclusions as to the safety of the five hormones when used in accordance with good veterinary practice, by asserting that JECFA's recommendations could not achieve the level of health protection considered appropriate by the EC. The EC seems to suggest that it has conditioned its ability to conduct a risk assessment on these five hormones on whether the available scientific data from JECFA and other sources meet its appropriate level of protection. There is no basis for this approach in the text of the *SPS Agreement* or WTO jurisprudence. The EC confuses the notion of the insufficiency of the relevant scientific evidence with a WTO Member's right to establish its own appropriate level of protection.

4.265 The ability to conduct a risk assessment cannot hinge on a Member's appropriate level of protection. Such an approach undermines the basic logic of the *SPS Agreement*. The EC's approach would allow Members arbitrarily to set their level of protection so high that they could effectively exclude from the pool of relevant scientific evidence any evidence that does not meet their chosen level of protection.

4.266 The Appellate Body has confirmed that Article 5.7 is intended to address "situations where little, or no, reliable evidence [is] available on the subject matter at issue". The EC has not demonstrated why it considers that the vast body of relevant scientific evidence on the safety of these five hormones from reputable sources such as JECFA and Codex have yielded unreliable scientific evidence. The EC also suggests that the simple passage of time is sufficient to invalidate previously-held scientific opinions but it does not provide any reasons why the JECFA studies or the Codex Standards should now be considered to be unreliable.

4.267 The EC has misconstrued its obligations under the *SPS Agreement* and has failed to establish that there is insufficient scientific evidence to conduct a risk assessment on the five hormones concerned.

(iii) Available pertinent information

4.268 Under the second requirement of Article 5.7 of the *SPS Agreement*, Members may only provisionally adopt SPS measures "on the basis of available pertinent information, including that from relevant international organizations as well as from sanitary or phytosanitary measures applied by other Members".

4.269 The EC has acknowledged that the risk assessments conducted by JECFA concerning the safety of these five hormones constitute "available pertinent information" that must be taken into account by the EC. The EC recognizes that there must be an "objective relationship" between the SPS measure at issue and the available pertinent information. However, the EC fails adequately to explain why it is imposing a "provisional" ban in the face of the safety assessments by JECFA and international standards adopted by Codex that attest to the safety of these substances.

4.270 The EC asserts erroneously that a Member may disregard the results of the risk assessments performed by the relevant international organizations because the Member concerned requires more information in order to meet a higher level of protection. This assertion stems from the EC's propensity to use its chosen level of protection to avoid its obligations under Article 5.7 of the *SPS Agreement*. This Article applies in cases where no risk assessment can be performed due to the lack of relevant scientific evidence. Therefore, the EC cannot claim that this provision entitles it to disregard scientific evidence from relevant international organizations on the basis that the EC requires "more information" in order to meet a higher level of protection.

4.271 Thus, the EC has failed to demonstrate that there is a rational relationship between its ban on the five hormones in question and the available pertinent information from JECFA, Codex and other sources.

(iv) Additional information and review

4.272 Pursuant to the third and fourth requirements of Article 5.7, a Member may not maintain a provisional measure unless it: (1) seeks to obtain the additional information necessary for a more objective assessment of risk and (2) reviews its measure based on this new information within a reasonable period of time. Thus, Article 5.7 imposes a burden on Members to make active efforts to gather the additional information necessary for the performance of a full risk assessment and then review the appropriateness of their measure within a reasonable period of time.

4.273 While the length of the reasonable period of time to review a provisional SPS measures may vary from case to case depending on the difficulty in obtaining additional information and the characteristics of the SPS measure at issue, Canada disagrees with the EC's suggestion that a Member's domestic legislative procedures may have an impact on the determination of the reasonable period of time.

4.274 It is a well-established rule of customary international law that internal law may not be invoked as justification for the failure to perform a treaty obligation. Accordingly, the length of the EC's domestic legislative process should not be a factor considered in the establishment of the reasonable period of time to review a provisional SPS measure. In cases where a Member imposes a total import ban, the reasonable period of time to review the measure should be such as to minimize the extent of the trade impact of this measure.

4.275 The EC has provided no explanation as to if and how it is seeking any additional information concerning the safety of these hormones and how it has reviewed its measure accordingly in the two years since the adoption of its new directive.

4. Conclusion

4.276 For the reasons stated in Canada's rebuttal submission and those contained in Canada's earlier submissions, Canada respectfully requests that the Panel reject the EC's claims.

I. ORAL STATEMENT OF THE EUROPEAN COMMUNITIES ON EXPERTS OPINIONS DURING THE SECOND SUBSTANTIVE MEETING

4.277 There are certain "procedural" aspects to this expert meeting which the European Communities would like to comment on before turning to the substantive results of this meeting. As you are well aware, the European Communities, during the selection process last year, had objected to the selection of Drs. Boobis and Boisseau as experts to this Panel. This mainly, because both have been involved in drafting and adopting the very same risk assessments which the European Communities has not accepted as valid basis for its measures regarding hormone treated beef, that is JECFA's risk assessments. The European Communities' concern was that Drs. Boobis and Boisseau would lack the objectivity required to give the Panel the advice needed to make an objective assessment of the facts in this dispute. Last week's meeting has confirmed that this concern was more than justified. It is unavoidable what Drs. Boobis and Boisseau have done, namely to defend the conclusions of the risk assessment they were involved in against any alternative conclusions which the EC's risk assessment has come to. We do not blame them for doing so. However, we do believe that their obvious partiality was not only unacceptable for the purpose of the role of experts in this dispute, it also made it necessary, at times, to enter into technical scientific discussions that we would probably all have rather avoided.

4.278 The European Communities does not wish to discredit in general the work which is done by JECFA and Codex, nor does it believe that these latter would wish to put into question in any way the EC's sovereign choices on the desired level of health protection. This is not a case "EC against JECFA". This is a case between Members of the WTO and it currently turns on the question whether a WTO Member has legitimately relied on its right under the *SPS Agreement* to base its measures on its own assessment of scientific evidence and available pertinent information, assessment which may deviate from that performed (but not necessarily adopted) by an international standard setting body. Objective expert advice of the kind that came from Drs. Guttenplan, Cogliano, Sippell and De Brabander, can explain what the scientific positions on either side are. It is not helpful, therefore, to have had (not only one but even two) scientific experts at this meeting who considered themselves to be representatives of JECFA.

4.279 It is not helpful either to have had JECFA representatives at this meeting who considered themselves to be scientific experts. Both Dr. Tritscher's and Dr. Wennberg 's role would have been to provide, in their capacity as secretaries to JECFA, factual information on how JECFA works, the way Dr. Miyagishima did for Codex. Instead, both have repeatedly overstepped their role and ventured into statements on the substance of the scientific issues. Although we are, for example, quite grateful for Dr. Tritscher's indiscretion on the origin of JECFA's reference to "potential genotoxicity" (she stated that it was because JECFA felt there was scientific uncertainty), we do not think that it was appropriate for her to provide information on the substance of the science or to assume the role of defending the substance of JECFA's work. And we certainly feel that Dr. Wennberg would have done better not to intervene on the issue of residue data used in the 1999 evaluation (on which she was obviously not informed) or to keep her opinion, for example on Radio Immuno Assays, to herself.

4.280 Let me end my comments on the procedural aspects of this expert meeting here by inviting the Panel to take them into account when it assesses all the different advice it has been given at this meeting.

4.281 I will now turn to the substantive results of this meeting and place them in the legal context. For the sake of this discussion, the European Communities accepts for a moment the assumption that your task in this dispute is indeed to assess whether measures taken to comply with DSB rulings and recommendations are consistent or not with Articles 5.1 and 5.7 of the *SPS Agreement*. However, we will come back to this at a later stage.

4.282 The United States and Canada claim that the European Communities has violated Article 5.1 of the *SPS Agreement* in re-adopting its ban on oestradiol-17β for growth promotion purposes. (I'll open a parenthesis here: this is not quite the way they put it as they believe the burden of proof is on the EC to demonstrate compliance. However, the EC strongly rejects this point, and I will also come back to that later. Fact is that they have raised a number of arguments as to why the EC allegedly violated Articles 5.1 and also 5.7 and therefore is not in compliance).

4.283 They argue essentially on two levels. First, that there is no risk assessment, supposedly because the EC Opinions of 1999, 2000 and 2002 failed to perform the second and third of the four steps usually done in a risk assessment on substances of this kind by the members of Codex Alimentarius Commission. Second, that the evidence put forward by the EC allegedly does not support the ban.

4.284 Last week's expert meeting has yielded a wealth of information which is crucial to dealing with these two levels of argument. Rather than repeating all the legal arguments as set out in our submissions, I will concentrate on where the scientific advice you got helps to clarify the issues.

4.285 On the first level of argument, we learned from the rather *unisono* statements of the experts. We have learned that while everyone (including the European Communities) accepts that in a risk assessment you may proceed in the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization, you only do that to the extent possible and necessary. In other words, how you proceed exactly is a function of the data you have available and of how your risk assessment is framed, namely by the mandate you have received from the risk manager. Thus, we learned from Drs. Boobis and Cogliano that data are never complete, but are or are not sufficient for the purpose of completing a risk assessment. We learned that this is a matter of judgment involving considerations on what sort of possible gap/uncertainty/insufficiency we are dealing with and whether that can be dealt with through interpretation or bridging tools such as safety factors and assumptions, or not. Most importantly, however, we learned that this judgment is informed – indeed, is framed – by the risk *manager*. It is the risk manager, as Dr. Miyagishima pointed out, who decides whether or not to carry out an evaluation and who factors into that decision the question of whether there are sufficient data. I draw your attention in this context to paragraph 19 of the Codex draft Risk Analysis Principles for the CCRVDF, which are about to be adopted. Paragraph 19 specifies that it is for the CCRVDF to provide "a qualitative preliminary risk profile as well as specific guidance [to JECFA] on the CCRVDF risk assessment request."

4.286 Finally, it is the risk manager, as several experts repeatedly confirmed, who decides on the acceptable level of risk, in other words on the level of protection. This informs for example concepts such as that of "appreciable risk", as Dr. Guttenplan explained in reply to your question. Let us not go into the whole concept of risk communication, but it is important for you to understand that risk assessors and risk managers – as two different instances of a risk analysis process – do not make decisions in isolation from each other. This has already been confirmed by the Appellate Body in the 1998 *Hormones* report.

4.287 This brings us back to the famous four steps of the risk assessment. If there is a risk management decision that the intended acceptable level of risk is "additional risk to the extent such a risk is judged 'insignificant' or 'non appreciable,'" here is what you do as a risk assessor: once you have identified that there is the possibility of an adverse effect, you go on and calculate whether and at what threshold the risk becomes "non appreciable" using safety factors and whatever other tools you have available to bridge possible gaps of knowledge. This is what JECFA has done.

4.288 If, on the other hand, there is a risk management decision that the intended acceptable level of risk is "no additional risk," the situation is different: as a risk assessor, once you have identified the possibility of an adverse effect and the possibility of its occurrence in real life, there is no point in going on and calculating a threshold, as no additional risk, however minimal, would be accepted. As a risk assessor you have done enough for the purposes of the risk assessment that the risk manager has asked from you. Essentially (I am saying essentially because the European Communities, as even Dr. Boobis had to confirm, has actually quantified exposure to the extent possible) this is what the EC risk assessors have done. Your experts have confirmed this, not least Dr. Boobis, who first advised you that the European Communities had not carried out a proper risk assessment and then qualified his reply by stating that it was based on the assumption that a threshold would apply. Where this is not the case, so he explained last week and in his written replies to Questions 11, 19 and 37, the remaining steps after hazard identification look quite different. In particular, a dose response assessment is unnecessary (see in particular reply to Question 37). However, as to what exactly the remaining steps are supposed to look like in a non-threshold scenario, neither Dr. Boobis nor the other experts gave you clear advice on that question. You heard statements that the European Communities failed to present new residue data or failed to refer to the problem of endocrine effects in its risk assessment or failed to present evidence on *in vivo* genotoxicity, all of which the European Communities proved to be wrong by pointing the Panel to the exact page where this issue was discussed or a study was referred to in the EC Opinions. Frankly, Chairman, one might choose to disagree with the conclusions the EC has come to, but to claim that the EC has not carried out a proper risk assessment is a bit of a joke, obvious to anyone who has actually taken pains to read the EC risk assessments (and, if I may add, to compare them to other relevant risk assessments).

4.289 So let me turn to the second level of argument, which turns on whether the evidence presented by the European Communities supports – or, as the Appellate Body would put it – sufficiently warrants a prohibition on oestradiol-17β. Chairman, I could go back to the details of all the adverse effects that the EC risk assessment has identified and that were at least in part discussed at last week's meeting. I could now launch into discussing everything that was said about old and new residue data, old and new detection methods, good veterinary practice and abuse, hormonal development of children and the value of epidemiological studies. But I think there is probably no better way of putting in a nutshell the controversy at the heart of this debate than the way Dr. Cogliano has done it. He said essentially "at the heart of the scientific disagreement here is the interpretation of data. JECFA's assessment felt that a threshold could be assumed even if there was some evidence on genotoxicity. Therefore they assumed there was a threshold. It seems to me that the EC is unwilling to assume a threshold, because of genotoxicity and because of low dose response and the fact that the shape of the curve cannot be defined with certainty. Those are the scientific arguments on both sides – depending on how you phrase the question, you will get a response of yes or no." On the question, of whether this disagreement is arbitrary or unreasonable, Dr. Cogliano answered by stating that "this is a longstanding area of disagreement for scientists since many years, the reason for the controversy being the assumptions that scientists bring to the risk assessment. It is an area of legitimate disagreement."

4.290 Even Dr. Boobis, who may have wanted to make you believe that JECFA's – that is: his – interpretation of the data is the only reasonable interpretation, had to concede that both genotoxicity and low dose response are issues that are a long way from being resolved. What better way to demonstrate this than the vivid debate between Dr. Guttenplan and Dr. Boobis on proof of *in vivo*

genotoxicity? What better way to say it than Dr. Boobis' reply to the EC expert's intervention on low dose response, when he stated "this is a major issue of scientific controversy. Dr. Vom Saal can point to so many papers which support his argument, but currently this is not resolved in the scientific community."

4.291 I could add to this now an account of the many things that were said last week about pre-pubertal children, where the advice you received from the Panel's experts ranges all the way from warning you not to feed your children broccoli (Dr. De Brabander) to stating that there is no problem whatsoever for hormonal substances despite evidence demonstrating that JECFA's calculations on endogenous production of hormones are actually wrong (Dr. Boobis).

4.292 But the point can already be made: what you should take away from last week's meeting is the following: First, the European Communities bases itself on evidence which well respected scientists, including some of your own experts (Drs. Guttenplan and Cogliano) understand to demonstrate direct genotoxicity of oestradiol-17β. Direct genotoxicity, not only for the EC risk manager but actually for most risk managers in this world (see Dr. Boobis' reply to Question 11) is a reason not to accept any added risk and therefore to decline setting a threshold. Second, the European Communities bases itself on evidence which is read by respected scientists – and, apart from Drs. Cogliano and Sippell this may well include most endocrinologists in the world – to mean that one actually knows precious little about what hormonal substances do at low doses, and in particular, what they do to especially sensitive populations such as pre-pubertal children. For the EC risk manager, and this may well be a position not shared by the risk managers in the US and Canada, this is a reason to decline setting any threshold.

4.293 The European Communities considers that it is not for this Panel to enter into the deep scientific theories and try to resolve the scientific controversies, to which you have become witnesses last week. The scientists have not managed to resolve it and you will not be able to do it with the legal provisions and tools you are supposed to apply here. Indeed, you are not asked to now come down on either side of the debate, apply your own – as Dr. Boobis would put it – "weight of evidence" approach, provide your own interpretation of how the data should be read. It is sufficient for you to ascertain that there is a genuine divergence of scientific opinions here, which may indeed – as the Appellate Body has put it – "indicate a state of scientific uncertainty"[19] and that the European Communities has relied on – and I quote the Appellate Body again – "divergent opinion[s] coming from qualified and respected sources"[20] as your own experts have confirmed. The US and Canada may think that this source may not (yet) represent "mainstream" scientific opinion (although one may well argue that there is at least equal balance between the different opinions) but this, as the Appellate Body teaches us, "does not necessarily indicate the absence of a reasonable relationship between the SPS measure and the risk assessment, especially where the risk involved is life-threatening in character and is perceived to constitute a clear and imminent threat to public health and safety."[21] There is no other indication that the European Communities may not have acted in good faith (may those who cherish protectionist theories go back to reading what the Appellate Body had to say about that).[22] Therefore, Chairman and Members of the Panel, your conclusion must be that the EC's risk assessment sufficiently warrants – that is to say reasonably supports – its ban on Oestradiol-17β.

4.294 This concludes my comments on the United States' and Canada's claim that there is a violation of Article 5.1 of the *SPS Agreement* as regards the EC's implementation measure on Oestradiol-17β. I should add that this also deals with the rather vague claim made by the United States and Canada that there would also be a violation of Article 3.3 of the *SPS Agreement*. "Vague"

[19] Appellate Body Report on *EC – Hormones*, at para. 194.
[20] Ibid.
[21] Ibid.
[22] Appellate Body Report on *EC – Hormones* at para. 245.

because it is not clear what they would be relying on with regard to oestradiol-17β. The standard adopted by Codex on this substance dates back to 1988 and is outdated, not only in the EC's view but also in the view of Codex' own scientific committee JECFA, which has re-evaluated the substance since. However, JECFA's updated assessment of 1999 has never been adopted as a standard. In any event, as is clear from the above, the European Communities who has a scientific justification not to base itself on the Codex standard, and also (not "or")[23] has a higher level of protection than that implied in the Codex standard, acted consistently with Article 5.1. of the *SPS Agreement.* Therefore, there is no violation of Article 3.3.

4.295 Let me turn to the European Communities provisional ban on the other five substances, progesterone, testosterone, zeranol, trenbolone acetate and melengestrol acetate (MGA). With regard to that measure the United States and Canada claim that there is a violation of Article 5.7 of the *SPS Agreement.* I will not go back to all legal arguments that have been exchanged between the parties on the four conditions that Article 5.7 of the *SPS Agreement* requires, but will instead concentrate on what the expert meeting has yielded in this regard, which mainly relates to the issue of sufficiency.

4.296 Obviously, you as the Panel wonder what to make of the fact that an international body such as Codex and its scientific committee JECFA, with regard at least to four of these substances, has considered that there is sufficient evidence to come to a conclusion on them, while the EC claims that this is not the case.

4.297 This brings us back to the debate touched upon earlier about completeness of data, sufficiency, gaps and scientific uncertainty. For all of those among us lawyers who love to think in clear cut-categories, this is a bit of a disappointment. The world of science clearly does not think in terms of definitive and provisional measures, of sufficiency and insufficiency of evidence. Data are never complete, as we learned; whether you can come to definitive conclusions on a risk assessment is a function of what data you have and how your risk assessment has been framed by the risk manager. Dr. Boobis, who emphasised several times how careful he was about choosing his words, certainly was careful when replying to the question of whether it was possible to complete a risk assessment on the five substances. He agreed with the European Communities that this was a question of risk management and then stated: "I can only speak for JECFA, not for the EC, we considered the data to be sufficient." Indeed, he speaks for a different set of data and against the background of a different decision on acceptable level of risk/intended level of protection! The EC's scientific committee worked on the basis of the most up to date research on these substances and against the background of the risk manager's decision not to accept any additional risk from residues in hormone treated-meat. Under these circumstances, the EC scientific committee, in the face of evidence indicating that there may be risks with regard to genotoxicity and in light of the scientific uncertainty regarding the low-dose response problem, was careful to conclude only provisionally on the existence of a risk, and to recommend further research. Who would have preferred a bold conclusion based on all sorts of gap-bridging assumptions, that these substances present a risk, and on the basis of that a definitive ban adopted by the EC regulator?

4.298 This concludes my remarks on the Article 5.7 claim, which has been shown to be unfounded. Let me add a brief remark, once again on the Article 3.3 claim made by the United States and Canada. The United States and Canada are relying on standards for zeranol and trenbolone acetate adopted in 1988, which are as outdated as the standards for progesterone and testosterone also dating back to 1988. Again, as is clear from the above, the European Communities who has a scientific justification not to base itself on the Codex standard, and also a higher level of protection than that implied in the Codex standard, acted consistently with Article 5.7 of the *SPS Agreement*. Therefore, there is no violation of Article 3.3.

[23] As the Appellate Body has put it so delicately, "Article 3.3. is evidently not a model of clarity in drafting and communication", see Appellate Body Report on *EC – Hormones*, para. 175.

4.299 These remarks of the European Communities attempted to help you place the results of last week's experts' meeting in the context of your analysis on the relevant provisions of the *SPS Agreement*. Before turning to my reservation on that exercise, which I stated in the beginning, let me make one final remark. It seems fashionable, in the debate on the *SPS Agreement*, to raise the spectre of regulators who close off their markets by putting never ending demands for more evidence on scientists on the basis of a declared need to prove safety. There is a danger for abuse of the *SPS Agreement* in this respect, no doubt. But there is another spectre out there, which is equally haunting: that the *SPS Agreement* would be abused by those who value market profit over safety. That those who do not bother to look into possible health concerns, referring, at best, to industry data that no member of the public has ever seen, would benefit from some sort of presumption of being right under the *SPS Agreement*.

4.300 With this, I have ended my opening remarks on the outcome of the expert hearing. Now, with regard to my earlier reservation: Chairman, we want to raise the question with you, why it is we are going through this exercise of looking into a violation of the *SPS Agreement*. As suggested in your e-mail we will come back to this issue in the second part of our opening statement when we discuss legal issues.

J. ORAL STATEMENT OF CANADA ON EXPERTS OPINIONS DURING THE SECOND SUBSTANTIVE MEETING

1. Introduction

4.301 Canada considers that the conclusions to be drawn from the expert meeting are that the ban on oestradiol-17β is not based on a risk assessment and the evidence is sufficient to conduct a risk assessment for the other five hormones. Canada understands that, in discussing the experts' advice, the parties may not introduce new evidence into the record and further that any statements made by the disputing parties' own experts should be viewed and assessed as an argument of the party concerned, rather than as evidence contained in free-standing scientific testimony.

4.302 The experts' advice is particularly pertinent where it addresses the scientific questions that are within the legal framework of this dispute, namely, whether the EC's ban on meat from animals treated with oestradiol-17β is based on a risk assessment appropriate to the circumstances, and whether there is sufficient scientific evidence to conduct a risk assessment for the other five hormones. The advice from the Experts on these claims was that the EC's risk assessment was not appropriate to the circumstances and that there is sufficient evidence to conduct a risk assessment for the other five hormones.

4.303 In light of the sensitivities surrounding public health and safety aspects of this case, the Experts' role was more significant than the legal questions imply. It is not the role of the Panel or even the Experts to pass judgment on the safety of the hormones, but this case also does not consist entirely of technical legal questions. These hormones have been studied extensively, and the studies demonstrate that they do not pose any real-world risk to human health and safety. Also, science evolves, methodologies and techniques improve, conceptions change, appreciation of hazards and risks in our environment alters, but no credible evidence has brought into question the safety of these hormones. Further, in the face of scientific uncertainty, inquiry does not end and public health is not managed on the basis of anecdotal observations, speculation and fear. Finally, risk assessors have developed rigorous, reliable and recognized ways to handle uncertainties responsibly.

4.304 The importance, therefore, of the contribution of the Experts is that they have collectively underlined and stressed these simple facts and have firmly deflected the EC's assault on the integrity of scientific methodologies and techniques that underlie all scientific inquiry and of organizations such as JECFA and Codex. The EC's claims to the contrary notwithstanding, even in the absence of

data that cannot be acquired, "with an understanding of biology, you can responsibly conduct a risk assessment."

2. The EC's risk assessments

4.305 The Experts' advice on the two legal issues was unambiguous. The EC risk assessment is not a complete risk assessment; it focused on hazard identification, some hazard characterization and no independent exposure assessment. And the evidence is sufficient for the performance of a risk assessment for the other five hormones. These answers should be sufficient to complete the assessment of the legal issues. Any remaining controversies have to do with matters more foundational and ancillary to these basic legal questions. These relate to the nature of the risk assessment exercise in general and specific issues of the genotoxicity and potential adverse effects on sensitive populations.

3. The nature of assessing risk

4.306 The Experts raised several issues that are relevant to evaluation of the EC's assessment, including the nature of risk assessment techniques and the appropriateness of these techniques in these circumstances.

(a) Hazard versus risk

4.307 Understanding the difference between "hazard" and "risk" leads to a better understanding of approaches to risk assessment and the steps within the kind of risk assessment appropriate in these circumstances. This understanding also illuminates the central deficiency of the EC's approach to these growth-promoting hormones.

4.308 Calling a substance a hazard reveals something about its intrinsic properties, its capacity to cause adverse effects. For example, some substances have the intrinsic capacity to cause cancer because of the way they interact with human cells. The role of IARC, the US Report on Carcinogens (RoC) and the first step of the four-step risk assessment technique is to identify and classify such substances. However, calling a substance a hazard says nothing about whether adverse effects will occur in any given scenario involving that substance. IARC and the RoC stop after identifying the hazard and provide no information on the likelihood that any particular exposure to the substance will lead to cancer. It is the role of other agencies to complete the analysis of risk.

4.309 Risk is not only about whether a substance is capable of causing adverse effects, but is also about identifying the likelihood that a given exposure to a substance will cause adverse effects. Whereas the identification of a hazard is a qualitative assessment about the intrinsic capacities of a substance, the evaluation of risk often involves a quantitative evaluation. It is, therefore, not sufficient for the EC simply to identify these substances as posing a hazard. The EC's risk assessment must say something about the risks from the specific uses of the hormones as growth promoters.

(b) Risk versus thresholds / dose-response assessments

4.310 There are many substances for which not all exposure scenarios lead to the quantification of risk, because there are exposures, known as a threshold, below which there is no risk of adverse effects. In these cases, identifying a substance as carcinogenic precludes neither further evaluation of it nor the identification of safe exposure levels. The issue is not the quantum of risk, but whether a given exposure may have adverse effects, which is the role of dose-response assessments. A dose-response assessment allows one to "characterize a hazard" by revealing the dose required for adverse effects to occur.

4.311 For substances known to be carcinogenic through a direct genotoxic mode of action it is assumed that there is no threshold below which no adverse effects will occur, making a dose-response assessment unnecessary. Even in these rare cases, however, risk assessors may conduct a dose-response assessment because the effects of most mutations are not deleterious. A risk assessor is not justified in skipping a dose-response assessment for substances known to have a threshold. The Experts believed that in this case a dose-response assessment should have been conducted.

(c) Integrity of the international risk assessment system

4.312 The scientists, regulators and administrators who work in the international standard setting system for veterinary drugs act with professionalism and integrity. The four-step risk assessment process – hazard identification, hazard characterization, exposure assessment and risk characterization – is time-tested and universally adopted at the international and national levels. To question these methodologies with respect to the evaluation of one substance calls into question the work of risk assessors everywhere.

4.313 Advanced techniques, such as conservative assumptions, ensure that standards based on them address global regulatory needs. The basic principle of every risk assessment is to be protective of the most sensitive sub-populations. This is accomplished through the use of the most sensitive adverse effects in identifying the threshold for adverse effects, the use of safety factors, and overestimation of the intake of residues in determining exposure.

4.314 Since science evolves and our understanding of science evolves, the risk assessment process remains flexible. The fact that new questions can be raised at any time does not stand in the way of decision-making, but decisions remain subject to review. Members of Codex and JECFA are invited to submit new data and call for a review of existing standards if they believe that they are no longer sufficient. Since the Members share responsibility for ensuring that standards are continually updated to reflect emerging data, the failure of one Member to provide new data and seek review of an existing standard can not be ascribed to the failure of the standard-setting system itself. The EC has chosen not to avail itself of the review process for these international standards.

(d) Scientific uncertainty, appreciable risk and zero risk

4.315 Because science cannot guarantee with 100% certainty that a substance will never cause adverse effects, risk assessments are not expressed in terms of absolute certainty. This is not to acknowledge that there are risks, but to acknowledge that we can never definitively say that there <u>are</u> no risks, or that the risk is zero. This uncertainty is reflected in the term "no appreciable risk", which is not the subjective value judgment of the risk assessor, but simply that unknowable and unquantifiable residual risk inherent in living. Several Experts expressed this uncertainty in quantitative terms, not to quantify real risks from veterinary drugs, but to illustrate just how small these risks, if any, really are.

4.316 Risk managers who require guarantees of "zero risk" are imposing unreasonable and unachievable demands. The methodologies do not exist to provide those kinds of assurances, particularly for substances that are endogenously produced in the human body and available from other dietary sources. Although uncertainty will be present in any scientific inquiry, risk assessors take that uncertainty into account and, when possible, eliminate it. The result is risk guarantees that leave room for theoretical risk, but not more.

4. Specific scientific issues

4.317 The two most significant scientific conclusions made by the SCVPH were that oestradiol-17β is carcinogenic through a genotoxic mode of action and that there are potential adverse hormonal effects for sensitive populations.

(a) Evidence of carcinogenicity through genotoxic mode of action of oestradiol-17β

4.318 The SCVPH declined to conduct a dose-response assessment in any of its three opinions as a result of its conclusion that oestradiol-17β was genotoxic *in vivo*. That conclusion is not justified by the available data. It is necessary to understand the mechanism – or mode of action – through which a compound can cause cancer in order to assess the risks. Since compounds capable of causing cancer through a hormonal mode of action exhibit a threshold below which cancer will not occur, the risk of cancer is dependent on exposure at doses higher than the threshold. It is not in dispute that oestradiol-17β is carcinogenic through a hormonal mode of action, for which there is a threshold. It is disputed that oestradiol-17β is also carcinogenic through a genotoxic mode of action.

4.319 While there is evidence from *in vitro* studies that oestradiol-17β has "genotoxic potential", to conclude that it is carcinogenic through a genotoxic mode of action requires confirmed *in vivo* evidence of genotoxicity. This has not been confirmed due to the existence of defence mechanisms such as metabolite inactivation, excretion and anti-oxidant systems, DNA repair mechanisms and natural (homeostatic) controls. These mechanisms are redundant and effective because cell damage occurs quite regularly and naturally in the human body. The "genotoxic potential" of oestradiol-17β can be observed *in vitro* because these mechanisms are unavailable, suppressed or overwhelmed. It is not observed *in vivo* due to the existence and correct functioning of these mechanisms. Studies relied upon by the EC to demonstrate genotoxicity *in vivo* simply confirm that, if thresholds for adverse effects are overwhelmed, there can be dramatic results.

4.320 The Experts confirmed that oestradiol-17β is not genotoxic *in vivo*, let alone carcinogenic through a genotoxic mode of action, and the EC provided no evidence whatsoever that oestradiol-17β can cause mutations leading to cancer. It is also not just an issue of judging one scientist's opinion over another, but that the EC's studies are simply not credible enough to support any other interpretation on the weight of all the evidence. The carcinogenicity of oestradiol-17β is therefore considered to be subject to a threshold. Since the SCVPH made an erroneous interpretation of the evidence related to thresholds for oestradiol-17β, it was wrong not to conduct a dose-response assessment.

(b) Potential adverse hormonal effects for sensitive populations

4.321 The Experts also advised on the potential for adverse hormonal effects, particularly in prepubertal children. They pointed to homeostatic control mechanisms that adjust endogenous production of hormones in response to exogenous exposure and advised that exogenous hormones are indistinguishable from endogenous hormones. While these controls may not be 100% effective, the assessment of risk must take them into account. The Experts also advised that the bioavailability of a substance is important and that it can be substantially less than what is orally ingested. While there was speculation that hormones may be more bioavailable in children than in adults, there is no evidence for this.

4.322 Some Experts considered that there is no direct evidence of adverse effects on prepubertal children from exposure to hormones from treated meat. Others did not contest this conclusion but claimed it had not been properly investigated. The "indirect evidence" cited, such as epidemiological studies related to puberty, simply does not implicate hormone growth promoter residues due to the problems of "confounding" factors. The EC had no explanation as to why, if minute increases in

hormones have such significant effects, prepubertal children do not suffer adverse effects from consuming eggs, meat and milk. The explanation provided by others is that metabolic and homeostatic control systems are functioning as they were designed and no adverse effects occur.

4.323 There are also questions about claims that exposure to low doses of oestradiol-17β *in utero* carries a risk of breast cancer in adult life. In light of the high amount of oestradiol-17β produced daily by pregnant women and the low amount consumed from treated meat, the dose of oestradiol-17β to which the fetus is exposed is hardly low, and any incremental exposure from growth promoter residues is about as negligible as one can get.

4.324 The SCVPH also did not evaluate the potential for endocrine disruption in prepubertal children, but limited itself to an exposure assessment. It relied on data derived from an analytical method that has not been validated, one that has resulted in inconsistent estimates. It made dubious assumptions about bioavailability in children. In the end, it failed to evaluate potential adverse effects by not performing a dose-response assessment. Instead, it presumed adverse effects from exposure to hormones and speculated about the ratio of daily production in prepubertal children to exposure from treated meat. However, one cannot adequately assess risks without assessing exposure from normal food consumption. At least one Expert indicated that based on consensus levels of hormones in children JECFA's ADI would still be protective of sensitive populations.

5. Issues related to good veterinary practice

4.325 There was little discussion at the Experts meeting of issues relating to compliance with good veterinary practice, but a few points can be highlighted. First, the Experts clarified that mechanisms exist for testing meat and meat products to determine compliance with established MRLs. Second, since analytical methods for detecting residues need only be sufficient to identify whether residues exceed established MRLs, the availability of new and more sophisticated analytical methods for detecting residues is largely irrelevant when there is an established MRL with a validated detection method. Third, there are no new residue data, no reason to believe the residue data relied upon by JECFA are insufficient, and no reason for existing residue data to be recalculated simply because new methods have been developed. Finally, Dr. de Brabander's written statement that no control measure short of a complete ban can adequately protect against misuse and abuse is of questionable applicability to Canada in light of his admission that he has no knowledge of control measures in Canada.

6. Conclusion

4.326 The results of the meeting with the Experts are clear and consistent on the key issues. The Experts unanimously advised that the EC did not perform a risk assessment consistent with appropriate methodologies and that scientific evidence was sufficient to allow the performance of a risk assessment for the other five hormones.

K. ORAL STATEMENT OF THE EUROPEAN COMMUNITIES ON LEGAL ISSUES DURING THE SECOND SUBSTANTIVE MEETING

1. Introduction

4.327 The European Communities made a reservation in its statement yesterday when it questioned the point of going through this exercise of looking at the possible violation of provisions under the *SPS Agreement*. I am afraid that we have to postpone our discussion of that issue once again, to the end of this meeting, as it seems more important at this stage to respond to the Panel's request to clarify a few issues about the *SPS Agreement* and its application to the facts of this case. This is without

prejudice to our position on the provisions of the *SPS Agreement* which, if any, might be invoked against our measures.

2. Article 5.1 of the *SPS Agreement*

4.328 Let us start with the main violation found by the Appellate Body in the original *EC – Hormones* case, Article 5.1 of the *SPS Agreement*. The first point to make is that the situation today is very different from that which confronted the Appellate Body in 1998.

4.329 The Appellate Body had found that the old risk assessment performed by the European Communities was not specific enough to address residues in meat treated with hormonal growth promoters.

4.330 The optimal way to remedy that would be to establish a quantitative dose response relationship. However, the scientists last week have agreed (even though we did not need them to tell us) that this is not possible to perform because the necessary studies would entail, as the 2002 US Carcinogenesis Report says, conducting studies of long term human exposure and cancer incidence in very restricted environments which will be able to eliminate with confidence confounding factors in the initiation and promotion of cancer over a long latent period.

4.331 Visualize the study: a perfect place would seem a prison where you have a sufficient number of very long term prisoners living in identical conditions, half of whom would eat non-hormone treated beef and the other would eat hormone treated beef. Even under these circumstances, which can not possibly be more restricted, the results of the study would be rebuttable due to differences in the past exposure history of those in custody. You may visualize another situation where you have a sufficient number of newly born children with whom you perform a similar experiment for about 30 years. Do I need to go on?

4.332 In the absence of such studies we had to follow an alternative approach which is also acceptable under the *SPS Agreement*. Let's review what we have done and some important knowledge that we have acquired:

4.333 First, we now have sufficient scientific evidence that oestradiol-17β is genotoxic. This is not a theoretical risk, it is not negligible and definitely not "zero", it is a real risk however minimal.

4.334 Second, we have sufficient evidence that endogenous production of natural hormones by pre-pubertal children is by many times less than what was originally thought to be the case.

4.335 Third, most of the scientists have agreed that the dose-response curve cannot be defined with certainty for low exposure to these substances.

4.336 Fourth, there is sufficient evidence, which is consistent with the observation that already exposure from background endogenous production can lead to cancer;

4.337 Fifth, we know today that the old data used by the defending parties and JECFA and the method by which they have been collected, are questionable or no longer valid (*e.g.* depletion data produced with method of analysis not apt to detect metabolites);

4.338 Sixth, there is a sufficient body of evidence indicating increased rates of cancer in the US and Canada which is consistent with the argument that residues of meat treated with these hormones can contribute to these higher rates.

4.339 Seventh, we know that under realistic conditions of use, good veterinary practice cannot be respected in the administration of hormones in the US and Canada and this invalidates the ADIs and MRLs (as Dr. Boisseau confirmed last week).

4.340 These things we did not know back then in the 1990s, but do know them now. Last week we have heard that there is a difference of scientific views and of interpretation of data about some of these issues, but that this difference is not arbitrary and indeed reflects genuine scientific uncertainty. In light of this, it is not indispensable that the third step of the risk assessment, the exposure assessment, is performed in a quantitative manner.

4.341 With these data the European Communities has conducted a qualitative dose-response assessment and has come to the conclusion that residues of hormone-treated meat will constitute an added risk to human health. As the Appellate Body has explained in 1998, risk is not measured in the laboratories but in the real world where people live and work and die.

4.342 In conclusion on this point, we believe that the European Communities performed a risk assessment as appropriate to the circumstances and the very nature of these substances, and therefore the ban on oestradiol-17β is based thereon – that is: sufficiently warranted by that risk assessment.

4.343 Before turning to some comments on other SPS provisions, I would like to stress the important point that we have made. A proper risk assessment can come to the legitimate conclusion that there are gaps in knowledge. This is expressly recognized in point 11 of the General Working Principles for Risk Analysis of Codex Alimentarius Commission. JECFA's risk assessment bridges all knowledge gaps and scientific uncertainty by assumptions in favor of allowing the use of hormones in growth promoters.

4.344 It seems that the US and Canada do not accept that a proper risk assessment can conclude that there are gaps and scientific uncertainty. For example, the US relies on a contention, at para 56 of its statement of yesterday, that a risk assessment must fully address the four "mandatory" steps (and it claims that the European Communities has not done so).

4.345 There is no basis for this. Article 5.1 of the *SPS Agreement* states that a risk assessment must be "appropriate to the circumstances" and *take into account* techniques developed by international organizations. As the European Communities has so often explained, and the experts have confirmed, the four steps of the Codex guidelines only need to be taken where possible and necessary. A qualitative assessment of the exposure of the kind performed by the EC must be acceptable. Our exposure assessment is not worse than that performed by the defending parties and JECFA, because both are based on assumptions and extrapolations from data on animal experiments to human beings.

4.346 It seems that the US and Canada would like to make it almost impossible for the European Communities to conduct a risk assessment they would ever accept. If they were to succeed with this tactic, however, the result would not be more authorizations but more provisional measures under Article 5.7 SPS.

3. Article 3.3 of the *SPS Agreement*

4.347 There has also been mention of Article 3.3 of the *SPS Agreement*. The argument is not clear but the European Communities would like to make a couple of important points. First, WTO Members have a sovereign right to set a higher level of protection than reflected in international standards. Article 3.3 only requires Members to have a scientific justification for their measures reflecting this higher level of protection, not for the higher level of protection itself.

4.348 Another point that needs to be made is that Article 3 of the *SPS Agreement* applies to standards and measures, and does not require Members to accept risk assessments by organizations such as JECFA. Accordingly, the fact that JECFA may have made a different risk assessment, which is outdated by today's standards and reflects a lower level of protection is not a basis for holding the EC risk assessment to be inadequate. In any event, the European Communities has shown that its measure has the necessary scientific justification and aims to achieve a higher level of protection. For this reason we fail to see the relevance of Article 3 SPS as a basis for the claims of US and Canada in this case.

4. Article 5.7 of the *SPS Agreement*

4.349 Similarly, the fact that JECFA could carry out risk assessments on the five other hormones, is not a reason for holding that the European Communities cannot adopt provisional measures based on Article 5.7 of the *SPS Agreement*. For JECFA, the information is apparently sufficient to conduct risk assessments; for the European Communities it is not. Even Dr Boobis agreed (and the US misrepresents his position at para 35 of its statement yesterday morning).

4.350 The US is also wrong to say (in para 6 of its statement) that the European Communities has failed to review the provisional bans within a reasonable time. The European Communities is in fact now conducting such a review once again.

5. Article 5.5 of the *SPS Agreement*

4.351 There have also been suggestions that the EC ban on oestradiol-17β (and the provisional prohibition of the other five hormones) are unreasonable or arbitrary in view of the large amounts of hormones that human beings are already exposed to from many different sources. Here again, we are not sure what the argument is. We cannot see how compatibility with Article 5.5 SPS is relevant to this case since no violation of this provision has been invoked by the Defendants. But even if it were, we would remind you of the interpretation of the Appellate Body of this provision. You cannot compare natural presence of these substances in a great many products with added risk from hormone-treated meat.[24]

6. Conclusion on the *SPS Agreement*

4.352 Chairman, Members of the Panel, our review of the possible relevance of the *SPS Agreement* has been somewhat cursory. Our problem is that we do not know what we are accused of. The US and Canada have not set out their claims in a Panel Request and their arguments criticizing our measures are varied and wide-ranging. We would be happy to discuss these issues in more detail if only we would be told exactly what it is we are doing wrong, because it is scientifically unsound and arbitrary.

7. Concluding statement of the European Communities

(a) Introduction

4.353 The European Communities would first of all thank you again for the professionalism and objectivity with which you have conducted these proceedings. Let me just recall that it was more than a year ago that we met for the first time to discuss the main claims of the European Communities against the US's s and Canada's illegal unilateral determination of the alleged inconsistency of the EC's implementing measure and, based thereupon, their illegal continuation of the sanctions against the European Communities.

[24] See para.221 of the Appellate Body Report on *EC – Hormones*.

4.354 The European Communities has explained in detail why in order to resolve these disputes it is not necessary for you to address the scientific issues related to the use of hormones as animal growth promoters. Chairman, Members of the Panel, you have nevertheless decided to look at these scientific issues. And we are the first to acknowledge that the scientific debate has not facilitated your life. As we have learned, the questions related to the use of these hormones are subject to a longstanding legitimate scientific debate amongst scientists with respected and reasonable arguments on both side.

4.355 However, one bottom line with which probably everybody will agree is that these hormones do not improve your health. These hormones are animal growth promoters but not health promoters. Instead we discuss scientific issues such as genotoxocity, mutagenicity, carcinogenesis, DNA repair mechanism, the risks of early puberty to our children, obesity, cancer as well as abuse and misuse of these hormones. Whatever one may think about this, it does certainly not increase our appetite for meat.

4.356 Another bottom line, which can be safely drawn, is that these hormones present a hazard and potentially a risk. Now, I agree that this is where the controversy starts. But whatever one may think about it as lawyers or consumers, neither of the scientists nor of the Defendants can reasonably argue that there is no potential risk related to the use of these hormones as growth promoters in cattle. Instead, we have heard a lot of talk about "thresholds", "appreciable risk" or "acceptable risk". But whether a risk is appreciable or not, whether a risk is acceptable or not, it still remains a risk. And contrary to what the defending parties have argued yesterday this is not a theoretical risk. No, the risk is real, however minimal it may be.

4.357 Why should we accept such a risk? Why should we expose our public to an additional risk to human health? Indeed, Chairman, Members of the Panel, we have heard repeatedly that we should not care about the addition of the natural hormones since they are also present in natural food, such as broccoli, milk, eggs or butter or produced endogenously. But the question persists why we should add on top of this an additional burden on the consumer without any health benefit in return. It is true that we all take risks in life whether we drive with a car, or when we take the plane or if we drink a glass of milk. However, we take these risks because we also see the benefit. Driving a car is comfortable, taking the plane is fast and milk contains a lot of vitamins. Yet, the story is different with hormones used as growth promoters in cattle. Here the risk is on the consumer. He has to face an additional health risk by being exposed to higher hormone levels. But he has no additional health benefit. Thus, from the perspective of a public health regulator, the risk/benefit calculation does not speak in favour of the use of these hormones either.

4.358 If at all, one may argue that the issue of not allowing hormones as growth promoters in cattle while we allow our children to drink milk is a matter of consistency. However, that would also be a very superficial view of the issues at stake. As we have explained yesterday and as the Appellate Body has already decided, one cannot compare these two things. On the one hand, we talk about natural food products that are part of our daily life over centuries and where there is a concrete risk/benefit for the consumer. On the other hand, the use of hormones in beef is an unavoidable risk which does not bring any advantages to public health.

4.359 How can this be better exemplified than by looking at our children. Children are the most sensitive part of the population and we must protect them wherever we can. There is a lot of uncertainty about how the mechanism of hormones in these children work but one can be sure that doubling the oestradiol doses – as would be the case by allowing hormones in beef – will have an effect. One of your experts, Dr. Sippell, has confirmed this pointing to the examples of early puberty or obesity. We should take his judgment very seriously when he drew the conclusion of the scientific hearing that he is "very concerned". Whatever toxicologists or veterinarian may have to say we should take this testimony of a paediatrician very, very seriously.

4.360 This brings me to one last point in this introduction which is about misuse and abuse of hormones as growth promoters. It is already striking that we always refer to "Good Veterinary Practices" even though no veterinarian or other trained health professionals is involved in the use of these hormones in the United States and Canada. As they are sold freely over the counter to farmers you will admit that controlling the correct use of these substances is difficult under these circumstances. It should strike us all that one implant contains the amount of hormones contained to up to 10,000 carcasses of animals. The European Communities has assessed what happens if these implants are misused and, indeed, there exists concrete evidence on this in the United States and Canada.

(b) The scientific debate

4.361 Let me now turn briefly to the outcome of the scientific debate regarding the use of these hormones as growth promoters in cattle. The European Communities is still puzzled by the United States' and Canada's attempts to present this debate as if there were only one single monolithic opinion in the scientific world on the safety of these hormones. This serves the US's and Canada's purpose but it is not objective.

4.362 It is true that we are all sometimes tempted to provide easy answers to difficult questions. And, certainly, this natural reflex is made even easier in the face of scientists who are able to "quickly dismiss" scientific evidence that they have not taken into account in the first place.

4.363 What is important for your decision, however, is to look at the differences and to see whether these differences are scientifically legitimate. The European Communities has never claimed that its scientific findings are the only valid ones, unlike what the United States and Canada have done. However, what the European Communities has repeatedly insisted upon is that its scientific views and its risk assessment are appropriate to the circumstances and that they come from respected and legitimate sources. One may not like the EC' conclusions but one cannot ignore or discredit them either.

4.364 It also appears sometimes ironic to present the EC' risk assessment in opposition to the JECFA's assessment. There is no doubt that the JECFA assessments have been based on outdated data since despite its assessment in 1999 this does not mean that the data also come from the 90's. Rather the JECFA representative admitted that they only review data as they receive them and in this particular case they had only received data from the FDA some of which date back to the 1960s. Despite the general acknowledgement that science is constantly moving forward and reveals new evidence this is an astonishing procedure itself which, again, we leave to your discretion on how you take this into account. A second undisputable issue is that JECFA's (and indeed the United States and Canada's) approach to risk is different to the one by the European Communities. JECFA has set thresholds in order to minimize the risk, the European Communities has prohibited the use of these hormones in order to exclude avoidable risks.

4.365 These are two completely different risk management decisions. Both are legitimate and we are, therefore, not criticizing JECFA for what it has done. However, we also cannot be blamed for deviating from JECFA's approach. It is ultimately the responsibility of the regulator or risk manager to decide what level of risk he wants to accept, and as I have indicated earlier, this is a very complex decision to which no easy answer can be given.

4.366 Let me then turn to our puzzlement by the United States and Canada's characterization of the scientific debate. We mentioned already yesterday that they very selectively refer to the scientific evidence in order to make their case. Chairman, Members of the Panel, we trust that you have a better recollection of what was actually said.

4.367 Let me just give a few examples. The United States has stated that "the experts agree that the EC has not presented any scientific evidence that estradiol is genotoxic *in vitro* or *in vivo* at physiological levels". However, may I remind you about the lively debate between Dr. Boobis and Dr. Guttenplan on this particular issue where Dr. Boobis "quickly dismissed" a study that was co-authored by one of his expert colleagues. Isn't it simply disingenuous to present this debate as if "all experts agree" that there is no evidence? And I'm not even talking about the experts that have not expressed an opinion on this issue.

4.368 Another example is the US's statement that "the experts have confirmed that the evidence for each of the five hormones is sufficient to complete a risk assessment". This is again incorrect. First, some of the experts have not even expressed a view on this. And even Dr. Boobis, who the United States often likes to rely on has merely stated that JECFA had enough information for completing a risk assessment whereas he could not say this for the European Communities. Again, as we have just explained, we all know the difference in these perceptions which is based on the fundamentally different approach by JECFA and the European Communities on how to deal with risks and whether or not it is appropriate to set a threshold in light of the possible direct and indirect genotoxcity of these substances.

4.369 A third and last example is Canada's today's statement that "nothing in what the Experts have written, nothing in what we have heard from the Experts (…) or the Experts have said demonstrates that there is any risk to human health, adult or child, old or young, man or woman, boy or girl, arising out of the correct use of these growth-promoting agents in cattle". It suffices to contrast this simplistic summary by Canada with Dr. Sippell's conclusion of last week that he is "very concerned" about the health of children if they were exposed to these hormones in beef. Again, we trust the Panel Members that they take into account what has actually been said by the scientists in their variety and not what the United States or Canada make out of it.

4.370 In this context, let me also refer to the closing statements by some of the experts during last week's hearing and which summarizes adequately the level of differences in the scientific world. Dr. Guttenplan stated that as regards young girls and boys we have to worry about the developmental effects of estradiol on them and that hormones sensitive cancer might be increased by raising the level of oestradiol. Dr. Sippell stated that we do not know enough about children and that the data are insufficient to be confident that the additional exposure from hormones treated beef poses no risk. Dr. Cogliano himself referred to the messiness of science and to the split within the scientific community. He also stated that these issues are not likely to be resolved any time soon. Finally, Dr. De Brabander even referred to other aspects related to the use of hormones as growth promoters such as animal welfare or environmental concern.

4.371 The European Communities considers that there is a bottom line that one cannot ignore. The scientific issues on which the European Communities and the United States and Canada disagree are not arbitrary but they are the result of a legitimate and genuine disagreement amongst scientists. This was the main result of the Panel' experts hearing. We do not believe that this Panel is in a position, or required, to resolve these long-standing scientific issues. Instead. we would urge you to acknowledge the legitimate scientific controversy and to draw the respective conclusions from it in resolving these two disputes.

(c) The context of the scientific debate

4.372 With these remarks, let me come back to where we ended last year after our discussion on the systemic issues under the DSU.

4.373 The European Communities would recall that these two disputes are still not about the *SPS Agreement* despite the extensive scientific debate that has taken place on the public health risk

related to hormones in animal treated beef. Chairman, Members of the Panel, the panel requests by the European Communities which provide the legal basis for these two disputes do not refer to any single provision under the *SPS Agreement*. Rather, as we discussed extensively last year, the European Communities has based its case against the illegal continuation of sanctions by the United States and Canada on systemic violations of the DSU, in particular Article 23, paragraphs1 and 2(a), Article 21.5 and Article 22.8.

4.374 As repeatedly stated, in order to resolve these disputes it is not necessary for you to make a substantive finding on the scientific issues. We have already set out that in our view the proper forum and the right procedural way to deal with these would be a compliance Panel under Article 21.5 of the DSU initiated by the United States or Canada.

4.375 This said, it is true that the European Communities has also made an alternative claim which requires you to address the substantive scientific aspects in order to determine that the original inconsistent measure has been removed and that the European Communities has addressed all the rulings and recommendations of the DSB.

4.376 However, this alternative claim has been only made "if, and only if" the Panel were to disagree with the European Communities on its systemic arguments under the DSU. Up until now, the Panel has not decided that this is the case. Therefore, the main claims and arguments as set out by the European Communities in its submissions are still valid and you are still called upon to take a decision.

4.377 Our discussion of the scientific issues may nevertheless be useful in respect of the main systemic claims made by the European Communities. I would just like to recall that one of the claims is that the US's and Canada's continued suspension of obligations is in violation of Article 23.1 and Article 22.8 of the DSU. This is so because by continuing to apply sanctions against the European Communities, the United States and Canada are unilaterally seeking to redress an alleged WTO inconsistency through the EC compliance measure. Furthermore, as you recall, in view of the requirements of Article 22.8 of the DSU, the European Communities has explained in great detail that its implementing measure must be presumed to be WTO-consistent since there is no multilateral finding to the contrary. This presumption is derived from the general principle of good faith whereby WTO Members are presumed to act in conformity with their obligations.

4.378 In this particular context, the European Communities considers that the scientific debate fully supports its proposition of a presumed compliance of its implementing measure. Indeed, since the scientific evidence demonstrates that the EC compliance measure is in actual compliance, it follows a *fortiori* that the lower standard of presumed compliance is also fulfilled.

4.379 Let me explain this aspect in more detail.

4.380 From the beginning of these two proceedings, the United States and Canada have tried to discredit the European Communities' compliance measure and its scientific foundations. Arguably, by this criticism the defendants have tried to undermine the European Communities' reliance on the principle of good faith (or in this case the presumption of compliance) under Article 22.8 of the DSU. And one has to admit that this litigation tactic by the United States and Canada was not completely unsuccessful because you felt the need to address the scientific issues related to the use of these six hormones as growth promoters in cattle notwithstanding the applicability of the general principle of good faith.

4.381 However, following the extensive discussion of the scientific issues, it is clear that this approach by the United States and Canada is not any longer sustainable. As we have seen last week, there can be no doubt that there exists a real and actual risk to public health related to the use of the

six hormones as growth promoters. The European Communities was therefore fully entitled to ban the use of these hormones in beef. And in legal terms, the European Communities was therefore also right in invoking the principle of presumed compliance within the context of its systemic claim under Article 23.1, 22.8 of the DSU.

4.382 The logic of this argument may also be further elucidated when the invocation of good faith is linked to the issue of burden of proof. The United States and Canada have attempted to make a prima facie case against the EC compliance measure. Yet, following the scientific debate the European Communities has refuted this prima facie case. The burden of proof is therefore still on the United States and Canada for questioning the European Communities' conclusion that the use of these six hormones for animal growth promotion is a risk to public health. The United States and Canada have failed to meet this burden of proof and they could not support their conclusions that the EC's ban on hormones treated beef was scientifically unsound.

4.383 We would like to recall that the European Communities also made violation claims under Articles 23 and 21.5 of the DSU that do not depend on the WTO-consistency of the EC's compliance measure. Rather these claims are directly linked to the US's and Canada's unilateral determination of the alleged inconsistency of the EC' compliance measure.

4.384 Finally, we have heard again this morning that the United States maintains that it could not have possibly made a "determination" that the EC's new ban is in fact WTO-consistent by the time the EC initiated these proceedings because the European Communities failed to provide all the necessary materials relevant to its measure.

4.385 This is a rather disingenuous characterization of the real facts and I will, at this stage not recall all our arguments that we have submitted to you. Let me just first point out that the United States erroneously keeps referring to a determination of WTO-consistency which it claims it could not make. The DSU neither requires nor forbids such "consistency determination". What the DSU prohibits, however, is the unilateral determination of a WTO violation by another Member.

4.386 Let me also recall, that while the United States in its view struggled to come up with a "determination" as early as from November 2003 they dismissed the EC compliance measure and explicitly stated in its Trade Policy Review of 2005 that "they failed to see how the revised measure could be considered to implement the recommendations and rulings of the DSB" . And in addition to that, since then the United States simply continued to apply its sanctions against the European Communities. There is no other way than to qualify this behaviour as an illegal determination of non-compliance. And, finally, it is also simply not true that the United States had been confronted with the evidence for the first time in 2003. All the underlying studies have been peer-reviewed and been published in journals and the European Communities undertook even an effort to discuss with the United States in Washington the scientific evidence. All this is on the record. The European Communities, therefore, cannot express again its puzzlement by the way the United States represents the facts in this dispute.

(d) Conclusion

4.387 For all these reasons, the European Communities would ask the Panel to find:

(a) First, that the United States' and Canada's continued suspension of concessions against the European Communities was inconsistent with the provisions referred to under Part I of the EC's first written submission.

(b) In the alternative, the United States' and Canada's continued suspension of concessions against the European Communities is inconsistent with the provisions set out under Part II of the EC's first written submission.

L. ORAL STATEMENT OF CANADA ON LEGAL ISSUES DURING THE SECOND SUBSTANTIVE MEETING

1. Introduction

4.388 Almost ten years ago, the DSB ruled that the EC ban on Canadian beef treated with growth-promoting hormones was inconsistent with the *SPS Agreement* because it was not based on a risk assessment. After the EC refused to bring itself into compliance, the DSB authorized Canada to impose retaliatory measures. The EC reaffirmed its ban in 2003, claiming that it was now based on a risk assessment in respect of one of the hormones and that there was insufficient scientific evidence to conduct a risk assessment for the other five. The EC launched this dispute, claiming: first, that the DSB authorization was no longer valid and that Canada had an obligation to suspend its authorized retaliatory measures; and, second, that if Canada does not, it has an obligation to bring a compliance case against the EC. The EC's DSU claims are wrong on the question of process and its alleged "compliance" with the *SPS Agreement* is unsupported by evidence and flatly rejected by the experts.

4.389 The EC's argument that Article 21.5 of the DSU provides that a complaining party has a legal obligation to launch compliance proceedings every time there is a "disagreement" as to compliance should be rejected for its systemic absurdity. The EC argues that, on the sole basis of an assertion of compliance by the EC, Canada should forego its rights under the WTO and launch dispute settlement proceedings. If the EC were to be found again in violation it could make another unilateral assertion of compliance and, if its procedural arguments prevail, force the parties into another dispute. Few things can be better calibrated to undermine confidence in WTO dispute settlement than the endless litigation loop that would result from this.

4.390 The EC's allegation of a breach of Article 22.8 on the basis that its unilateral assertion overrides the multilateral authorization of the DSB is also plainly wrong. Canada, having acted consistently with a DSB authorization, may not be found to be in violation of Article 22.8 on the sole basis that the EC has asserted that it has complied. To end the retaliatory measures in light of the disagreement as to its compliance, the EC must establish its compliance multilaterally. It is the EC's burden, since it seeks to overturn an existing DSB authorization. This case is therefore not about procedural lacunae in the DSU, but about the compliance of the EC measure.

4.391 The rest of Canada's submission addresses the legal requirements of the *SPS Agreement*. Canada makes the following preliminary observations. First, Canada's reference to exposure to hormones from other sources does not relate to the regulatory aspects of the "consistency" required by Article 5.5, but to the "appropriate circumstances" in relation to which the EC's risk assessment is conducted, pursuant to Article 5.1. The EC's position on the risks from these hormones is either irresponsible or disingenuous: if the hormones are as hazardous as it has claimed, the EC must conduct an assessment to determine in what doses there are health risks, regardless of how natural the products are; where it refuses to do so and insists that natural sources can be consumed every day but residues from treated meat cause adverse effects, scepticism about the EC's reasoning is warranted. Second, the EC seems to be saying that even if it loses, its ban will remain in place, justified not by Article 5.1 but by Article 5.7, because it will claim there are insufficient data to conduct a risk assessment. This makes it all the more important for the Panel to make findings about what constitutes "sufficient evidence", which is different from scientific uncertainty, minority opinion or speculations based on clinical observations.

2. The EC has not demonstrated that the relevant international standards are insufficient to meet its appropriate level of protection

4.392 The EC's measure is not justified under Article 3.3 because existing international standards are capable of achieving the EC's higher level of protection. While the EC alleges that these standards are insufficient and wrong, it has provided only unconfirmed evidence, considered within an artificially constructed level of protection of "zero additional risk".

4.393 Existing international standards have been developed using methodologies so widely accepted that to call them into question for these hormones calls them into question for other compounds as well. The EC misrepresents the level of protection inherent in these standards. For example, in light of other sources of exposure to the three natural hormones, standards for these hormones are such that it is not necessary to determine maximum allowable levels of hormone residue in meat, reflecting the conclusion that the ADI could never be exceeded simply by consuming treated meat. The EC considers the concept of "no appreciable risk" to be subjective and qualitative. However, that concept reflects scientific reluctance to guarantee zero risk in the case of very small, unquantifiable risk. Since the risk inherent in this concept is the risk from exposure to hormones at the level of the ADI, which includes exposure from all other sources, the risk from exposure to oestradiol-17β from treated meat is only 4% of the risk inherent in that concept. The level of protection achieved by international standards is therefore as close to zero as possible and reflects theoretical risk.

4.394 The EC claims that its ban is necessary because international standards cannot achieve its level of protection, which it has set at "zero additional risk" to get around the fact that risk management methodologies cannot provide for "zero risk". The EC therefore believes that it need do no more than establish that exposure to treated meat increases overall exposure to hormones, and then assume this automatically increases risk. This is based on incorrect assumptions that adverse effects will occur at anything close to normal levels of exposure to hormones and that levels of exposure to treated meat alter the level of hormones in the body sufficiently to alter the level of risk. However, since the EC provides no evidence that exposure to hormones from treated animals alters the risk that might already exist from exposure to other sources of hormones, it has not demonstrated that there are additional risks.

3. The EC has not demonstrated that its permanent ban on oestradiol-17β is based on a risk assessment appropriate to the circumstances

4.395 The EC claims that its reaffirmed ban on oestradiol-17β is now based on a risk assessment, but that assessment is not appropriate to the circumstances, does not identify and evaluate the potential for adverse effects from exposure from treated meat, does not demonstrate that exposure from this source causes cancer and does not demonstrate that sensitive populations are at risk from exposure from this source.

(a) The EC has not demonstrated that existing international risk assessment techniques are inappropriate to the circumstances

4.396 While the EC does not dispute that the four-step risk assessment process is appropriate to these circumstances, it does make two incorrect claims about the application of these steps in these circumstances. First, its claim that the *SPS Agreement* envisages a risk assessment that is "wider in scope" than the four-step process does not find support in the *SPS Agreement*. Article 5 addresses risk assessment techniques and not the separate and defined process of risk management. The EC reliance on sections of the Appellate Body ruling in *EC – Hormones* is also unjustified. There is a parallel between the four-step process and legal requirements to "identify adverse effects and evaluate the potential for their occurrence from exposure to hormones from meat from treated animals".

4.397 Second, the real reason the EC seeks to confuse the parameters of an appropriate risk assessment relates to its claim that the scientific risk assessment was justified in short-circuiting the process because of instructions from the risk managers related to "zero additional risk". A risk manager is not justified in instructing a risk assessor to skip certain steps of the assessment to serve risk management objectives. The risk assessment process is a scientific exercise that should arrive at the same scientific results regardless of the risk management framework within which it is conducted. The issue is therefore whether the EC's purported risk assessment unjustifiably departed from the four-step process.

(b) The EC has not demonstrated that the risk assessment on which its measure is based is appropriate to the circumstances

4.398 The EC measure is based on the three SCVPH opinions. While the EC has also submitted additional material, it has not attempted to demonstrate how this material constitutes a risk assessment. It is therefore the SCVPH opinions that must satisfy the four-step process. The Experts confirmed that it suffers from two critical flaws. First, the Experts confirmed that a dose-response assessment is a necessary component of a risk assessment, without which it is impossible to know the dose at which adverse effects will occur. In their own reviews, JECFA and others conducted dose-response assessments. Operating under the instructions to avoid "additional risk", the SCVPH declined to conduct such an assessment, concluding that the adverse effects from oestradiol-17β did not exhibit a threshold for adverse effects, and as such all exposure would lead to "additional risk". This conclusion is not justified by the scientific evidence.

4.399 Second, the failure to conduct a dose-response assessment led to the failure to complete a risk characterization, which corresponds to the requirement to evaluate the potential for the occurrence of adverse effects. The Experts disagreed with the EC that the SCVPH conducted a risk characterization. Assessment of risk from a substance in general was simply conflated with assessment of risk from a single source of that substance. After identifying oestradiol-17β as a hazard, the SCVPH concluded that exposure to it from treated meat poses additional risk. The finding that the original EC ban was not based on a "sufficiently specific" risk assessment applies equally this time, and the artificial construct of "zero additional risk" does not save it. The failure to complete these steps stemmed from mistaken interpretations of the scientific evidence, which the next section reviews.

(c) There is no evidence that oestradiol-17β is genotoxic *in vivo*

4.400 The SCVPH concluded that there is no threshold for adverse effects from oestradiol-17β on the basis of erroneous and scientifically unjustified interpretations of genotoxicity test results. While there is no dispute that oestradiol-17β is carcinogenic through a dose-dependent hormonal mode of action, and that there is evidence of "genotoxic potential", the SCVPH was wrong to conclude that oestradiol-17β is carcinogenic through a genotoxic mode of action. It ignored the fact that *in vitro* test conditions neutralize effective and redundant defence and repair mechanisms, meaning that *in vitro* genotoxicity must be confirmed by positive *in vivo* results. The "weight of evidence" is against oestradiol-17β being carcinogenic through a genotoxic mode of action. Other national and international regulatory bodies, as well as the Experts, have indicated this and the SCVPH has no credible evidence that all these experts are wrong.

4.401 While the EC raises the spectre of "scientific uncertainty" and "minority scientific opinion", the conclusion that oestradiol-17β is genotoxic *in vivo* is not supported by any reasonable interpretation of the available scientific evidence. For a contrary interpretation of the data to constitute a credible minority opinion, or for it to reflect "scientific uncertainty", there would need to be at least some evidence that could not be explained by the existing understanding of the issues.

According to the Experts, this is not the case. Any evidence there is that oestradiol-17β may be genotoxic can be explained according to common understandings of biological mechanisms.

(d) There is no evidence of adverse effects on the endocrine system

4.402 While the EC cites various revised estimates of blood concentrations of oestradiol-17β in prepubertal children, the issue is whether these estimates tell us anything about the implications of incremental increases in exposure from one particular source for the risk profile of prepubertal children. The JECFA analysis focuses on determining the level at which no adverse hormonal effects would occur in the most sensitive sub-groups of the population. The SCVPH did not evaluate the occurrence of potential adverse hormonal effects. It compared intake of oestradiol-17β from treated meat with this "new" daily production rate, concluded that the excess intake would exceed the daily production in prepubertal boys and then implied an increase in risk to prepubertal boys.

4.403 Apart from questions about the validity of the data and the justifiability of the assumptions, this approach suffers from basic methodological flaws. Since natural hormones are part of a normal diet, a risk assessment must take into consideration background dietary exposure. There is no evidence that there is no safe threshold for daily consumption of oestradiol-17β in part because of homeostatic control mechanisms. The SCVPH failed to consider the question of a threshold for safe daily intake because it did not conduct a dose-response assessment. The fact that background levels are lower than previously thought says nothing about the potential occurrence of adverse effects. Thus, as a result of a failure to conduct a dose-response assessment, the SCVPH has failed to evaluate the potential occurrence of adverse hormonal effects from exposure to hormones.

4. The EC has not, and cannot, demonstrate that there is insufficient evidence to conduct a risk assessment on the five other hormones

4.404 There are three legal issues concerning the interpretation and application of Article 5.7 in this dispute. First, the mere existence of scientific uncertainty does not imply that the scientific evidence is insufficient to allow the performance of a risk assessment. Techniques have been developed to address scientific uncertainty in the risk assessment process and these techniques can be seen in practical application here.

4.405 Second, the Appellate Body has clarified that "insufficiency" implies a relationship between scientific evidence and the ability to perform an "adequate" risk assessment. The EC suggestion that a WTO Member can determine what constitutes "sufficiency" of scientific evidence through the selection of its level of protection was already rejected by the panel in *EC – Biotech*. The advice sought by this Panel confirmed that the relevant scientific evidence is sufficient for the performance of a risk assessment. The "new" evidence provided by the EC does not call into question the JECFA risk assessments and the conclusion that these hormones are safe when good veterinary practice is followed.

4.406 Finally, Codex has a procedure whereby any Member can request a re-evaluation of a substance that has been previously reviewed by JECFA or for which a Codex standard exists. The EC has deliberately avoided using this procedure, despite its insistence that new information casts doubt on the validity of the Codex standards and JECFA risk assessments. One would expect the EC to invoke this procedure not only to protect its own citizens but also to protect the citizens of other countries that rely on Codex standards. Since the EC cannot demonstrate that the relevant scientific evidence is insufficient to perform a risk assessment on the other five hormones, it has not fulfilled the first condition of Article 5.7.

5. The EC has not demonstrated that the failure to follow good veterinary practice results in increased risk of adverse effects

4.407 The EC's purported assessment of the failure to respect good veterinary practice involves exaggerated and unrealistic overdosing scenarios and suffers from other flaws. First, despite the EC's assumption to the contrary, there is no evidence to suggest that there is an economic incentive to misuse growth-promoting hormones where their use is approved and controlled. The EC's experience with the abuse of banned hormones is not relevant to Canada where their use is permitted. There are in fact significant economic disincentives to overdose an animal as implants have been calibrated to provide an optimal dose. Second, even if some misuse occurs, the evidence presented by the EC does not support the conclusion that the misuse scenarios will lead to residue levels that create potential for adverse effects to occur.

4.408 Third, the EC has not evaluated whether unrealistic misuse scenarios occur in real life. It has ignored data from Canada's National Chemical Residue Monitoring Program, and has provided no evidence that Canadian meat contains hormones at levels exceeding the JECFA ADI. It depicts successful detection of non-compliance as a failure of controls, and misrepresents non-compliance as the norm. By ignoring the way in which hormones are actually used and the results of Canada's official residue monitoring program, the EC has failed to take into account "relevant processes and production methods" and "relevant inspection, sampling and testing methods" in the conduct of its so-called risk assessment on misuse and abuse, as required by Article 5.2 of the *SPS Agreement*. The EC's risk assessment does not meet the requirements for a risk assessment under the *SPS Agreement*.

6. Conclusion

4.409 The key legal questions at issue in this dispute have clear answers. For these reasons and those contained in Canada's earlier submissions, and the arguments and evidence submitted by the United States, Canada respectfully requests that the Panel reject the EC's claim that it has complied with the recommendations and rulings in *EC – Hormones*.

7. Concluding statement of Canada

4.410 It is natural, given the subject matter, that the parties on occasion may have shed more heat than light on the discussions. I hope that none of that has reflected poorly on us or on you.

4.411 The questions at issue are indeed emotive. I note for example that there was an entire section in the EC statement this afternoon about the protection of children. Certainly, there is nothing more important than protecting the health of our children. This is a concern to us as parents, brothers and sisters, public officials and, indeed, private citizens.

4.412 But it is essential to make a distinction between real concerns and the speculative references that have also been at play. There is no need to go into them in detail at this stage, but there have been a lot of them. That will surely present a difficult challenge as you proceed with this matter in your decision making.

4.413 Canada takes it as given that the parties, as democratic, law-abiding countries and entities, and also as public officials, all have as a principal objective the protection of public health and children's health. The question is not whether we protect the children – that's a given. We do so rigorously and without reservation. The question is how to approach doing so, and in doing so whether we are abiding by the law.

4.414 We have set out the law in detail, both on procedural issues and on substantive SPS issues, and will not repeat those points now. But the one point I wished to stress in closing is this: on

whichever side of the law you land, your decision will not harm the children. It would be a disservice to us all to cast the dispute in any other terms.

V. ARGUMENTS OF THE THIRD PARTIES

A. AUSTRALIA

1. Introduction

5.1 According to Australia, this dispute is about one fundamental question; whether the DSU provides that a Member's announcement of its compliance with DSB recommendations and rulings triggers an obligation on a retaliating Member to either (i) cease retaliation or (ii) initiate a new process for a multilateral determination of compliance.[25]

2. Opening Panel meetings for observation by the public

5.2 Australia contends that when parties agree not to follow the Working Procedures in Appendix 3, or parts thereof, it would be difficult for the Panel to justify a decision that goes against the wishes of the parties. In Australia's view, to do so would undermine a basic principle of dispute settlement whereby parties consult with each other and with the Panel and seek mutual agreement on the conduct of disputes, according to Article 12.1 of the DSU.[26]

5.3 Australia submits that the decision to open the meetings with the parties to the public would not pose a problem, in principle, to Australia. Australia was however concerned about the modalities of organising the meetings, equity of access and logistic issues. Australia was of the view that the opening of the Panel's meetings to the public should be subject to the provisions that allow for protection of confidential information.[27]

3. Whether the DSB authorization remains in effect

5.4 Australia argues that a Member's announcement of its compliance with DSB recommendations and rulings triggers an obligation on a retaliating Member to either cease retaliation or initiate a new process for a multilateral determination of compliance. Australia claims that as seen in Articles 22.1 and 22.8 of the DSU, the right to suspend concessions authorized by the DSB is temporary and conditional upon the respondent continuing to be in non compliance or upon a solution not being reached. According to Australia, by continuing retaliation in the face of a respondent's notification of compliance, a complainant is effectively challenging the measure(s) taken to comply. According to Australia therefore, in such a case it is for the complainant to invoke a compliance panel pursuant to Article 21.5 of the DSU.[28]

5.5 Australia contends that the suspension of concessions or other obligations is the "last resort" for Members invoking the dispute settlement procedures, as stated in Article 3.7 of the DSU.[29]

4. Article 21.5 of the DSU

5.6 Australia acknowledges that Article 21.5 of the DSU does not explicitly place the obligation to invoke a compliance panel on a complaining party. The text simply provides that in cases of disagreement over compliance such dispute shall be decided through recourse to the dispute

[25] Third party submission of Australia, para. 4.
[26] Replies by Australia to Panel questions concerning open hearings, question 1.
[27] Replies by Australia to Panel questions concerning open hearings, question 2.
[28] Third party submission of Australia, para. 5.
[29] Replies by Australia to Panel questions, question 5.

settlement procedure. Australia however argues that requiring a respondent to invoke a compliance panel against its own measure(s) constitutes an implicit unilateral determination of inconsistency by the complainant and undermines the presumption that Members act in good faith in taking action to comply with DSB recommendations and rulings.[30]

5.7 Australia further submits that this position is consistent with Appellate Body findings on the presumption of good faith in *Chile – Alcoholic Beverages*,[31] where the Appellate Body stated that Members of the WTO should not be assumed, in any way, to have *continued* previous protection or discrimination through the adoption of a new measure, as this would come close to a presumption of bad faith.[32] Australia also noted observations on good faith made by the Appellate Body in *US – Hot-Rolled Steel*[33]and *US – Line Pipe*.[34]

5.8 Australia thus points out that the fact that a complainant may have been granted temporary authorization to retaliate against a Member found to be in non-compliance does not change the fundamental application of the presumption of good faith. Australia stresses that disregarding the presumption in the specific circumstances of a Member announcing that it has taken action which it considers brings it into compliance would go against the design and underlying logic of the DSU.[35]

5.9 Australia posits that the DSU is explicit on the following points, which provide context for the interpretation of Article 21.5:[36]

- Members must not take unilateral action to seek redress for alleged violations of obligations or other nullification or impairment of benefits (Article 23).

- Instead, Members must have recourse to the DSU and abide with its rules and procedures (Article 23).

- DSU procedures, including those provided for in Article 21, must be used to resolve disagreements over compliance (Article 23.1).

- The suspension of concessions or other obligations is a "last resort" by Members and is temporary. That is, it is only authorized until compliance is achieved (Articles 3.7 and 22).

5.10 Australia contends that by refusing to invoke a "compliance panel", a complainant who disagrees with the respondent's announcement of its compliance allows the dispute to continue unresolved.[37] Australia argues that the longer the time period in which the United States did not take action under Article 21.5, the greater the firmness or immutability the United States made of its determination. Australia emphasizes that this is because a determination within the meaning of Article 23.2(a) of the DSU may be inferred once a certain amount of time has passed after communication by a responding party that it has complied and in which a complaining party continues to retaliate. According to Australia therefore, the longer the period of time that a complaining party

[30] Third party submission of Australia, para. 6.
[31] *Chile – Taxes on Alcoholic Beverages*, (WT/DS87/AB/R and WT/DS110/AB/R), paragraph 74, (emphasis in original, footnote omitted).
[32] Third party submission of Australia, para. 7.
[33] *US – Anti-Dumping Measures on Certain Hot-Rolled Steel Products from Japan* (WT/DS184/AB/R), para. 101.
[34] *US – Definitive Safeguard Measures on Import of Circular Welded Carbon Quality Line Pipe from Korea* (WT/DS202/AB/R), para. 110.
[35] Third party submission of Australia, para. 8.
[36] Third party submission of Australia, para. 9.
[37] Third party submission of Australia, para. 10.

continues its retaliation in the face of this communication, the greater degree of certainty there is for the inference that the retaliating party has determined that a violation has occurred, that benefits have been nullified or impaired or that the attainment of any objective of the covered agreements has been impeded.[38]

5.11 Australia argues that there is no procedure that a Member claiming compliance can invoke in order to obtain a multilateral determination of actual compliance. According to Australia, the possibility of a new dispute whereby the original respondent complains against the continued retaliating measures on the basis of actual compliance assumes that there is no obligation upon the retaliating Member to either initiate an Article 21.5 panel or cease retaliation after communication of compliance by a respondent, which is an incorrect interpretation of the DSU.[39]

B. BRAZIL

1. Introduction

5.12 Brazil claims that it files the present submission in light of its interests in the interpretation to be developed by the parties and the Panel in these proceedings. Brazil states that it will address what it considers to be the fundamental objective of the European Communities in the current dispute, namely to obtain multilateral recognition that it has fully implemented the recommendations of the DSB without having to bear the burden of proving how it would have effectively implemented those rulings.[40]

2. Opening Panel meetings for observation by the public

5.13 Brazil questioned the specific grounds and the DSU provisions on which the Panel based its decision to accept the parties' request to open the panel meetings for observation by the public. According to Brazil, transparency is one of the key issues in the DSU review process and constitutes an important element in the debate carried out by Members in the DSB meetings. As such, Brazil notes that the debate on transparency will largely benefit from any further clarification by the Panel as to the legal reasons which motivated its decision to open the meetings to the public.[41]

5.14 Brazil argues that a decision on whether or not to open panels' proceedings to the public relies solely on the WTO membership, in particular the DSU review process which is the appropriate *locus* to deal with issues regarding the Dispute Settlement Mechanism. According to Brazil, if panels were to decide on this issue, they would go beyond their mandate, playing a role that is exclusive to the WTO membership.[42]

5.15 Brazil further submits that the right to be present at or to watch a panel meeting should be granted first to WTO Members subject to the rules for third party participation set forth in Article 10 of the DSU. Brazil also contends that opening the meetings to the public would represent a reinterpretation of Article 14 of the DSU, signaling that there are cases to which confidentiality is not applied, such as Panel and Appellate Body meetings.[43]

[38] Third party submission of Australia, para. 10.
[39] Replies by Australia to Panel questions, question 4.
[40] Third party submission of Brazil, paras. 1 and 2.
[41] Oral statement of Brazil, para. 2.
[42] Replies by Brazil to Panel questions concerning open hearings, question 1.
[43] Replies by Brazil to Panel questions concerning open hearings, question 1.

3. Whether the DSB authorization remains in effect

5.16 In Brazil's point of view, the European Communities must prove that the new measure is in full compliance with the DSB recommendations. Brazil stresses that the European Communities' claim is based only on a unilateral sole assertion of compliance. However, a mere assertion is insufficient to prove compliance. Brazil submits that the European Communities may modify its legislation over and over and notify changes to the WTO without actually bringing the measures into conformity with WTO rules.[44]

5.17 Brazil considersthat if the European Communities argument were accepted, it would give the implementing Member the power to unilaterally dispel a previous multilateral determination authorizing suspension of concessions. Brazil contends that such Member would therefore be allowed to act as arbitrator, making use of a procedural artifice that could go on *ad infinitum*. Brazil notes that it would be absurd to have that practice accepted as the common practice in the implementation of WTO disputes. It would mean that a mere assertion that a Member has changed a measure found to be inconsistent automatically revokes a DSB authorization to suspend concessions, while exempting the Member from proving why and how the new measure complies with the DSB recommendations and rulings.[45]

5.18 Brazil submits that only in case of multilateral determination confirming that the European Communities has fully complied could there be grounds for consideration of whether the United States and Canada are in breach of Articles 23, 21.5, 3.7 and 22.8 of the DSU and Articles I:1 and II of the GATT'94, as claimed.[46]

5.19 Brazil argues that just as the initial imposition of suspension of concessions must be preceded by a DSB determination of non-compliance, the authorization for a Member to discontinue the suspension of those concessions can only be made by a DSB determination of compliance, be it for the initial suspension of concessions, or at a later stage for the lifting of the authorized suspension of concessions.[47]

5.20 Brazil posits that the right to suspend concessions is temporary and conditional because it can only be applied based on a multilateral authorization (Article 23.2 (c) of the DSU) and until the party in violation complies with the recommendations of the DSB or a mutually satisfied solution is agreed between the parties in the dispute (Article 22.1 and 22.8 of the DSU).[48]

4. Article 21.5 of the DSU

5.21 Brazil contends that the present situation is different from the one resulting from the relationship between Articles 21.5 and 22.6 of the DSU and it does not consider examples refered to by the European Communities regarding the *US – Subsidies on Upland Cotton* dispute,[49] and *Softwood Lumber*[50] disputes, to be applicable to the present proceedings. Brazil argues that the proceedings under Article 21.5 in those disputes had been already established at the time the implementing party requested the arbitration to determine the level of the suspension of concessions.

[44] Third party submission of Brazil, paras. 5 and 6
[45] Third party submission of Brazil, para. 8.
[46] Third party submission of Brazil, para. 9.
[47] Third party submission of Brazil, para. 20.
[48] Replies by Brazil to questions from the European Communities, question 3.
[49] *US – Upland Cotton*, WT/DS267/22.
[50] *US – Softwood Lumber VI*, WT/DS277/11.

Brazil stresses that in the current dispute, Article 21.5 proceedings and Article 22.6 arbitration are not "simultaneously ongoing", since no request for a compliance panel has been presented.[51]

5.22 Brazil submits that in the post retaliation phase, one should bear in mind that there is a multilateral authorization in effect. According to Brazil, a presumption of good faith in carrying out the implementing measure cannot by itself override a DSB authorization. That authorization should be revoked by a multilateral determination of compliance not by a unilateral declaration of implementation or a presumption of compliance.[52]

5. Burden of proof

5.23 Brazil posits that the party who makes a particular claim bears the burden of proof. Brazil further contends that by merely asserting that it has removed the inconsistency found by the DSB, the European Communities is not supporting its claim.[53]

5.24 Brazil also argues that the European Communities professes that no Member shall be 'judged' except through multilateral judicial proceedings.[54] However, Brazil notes that this notwithstanding, the European Communities serves itself with a "blank authorization" to determine unilaterally its compliance with WTO obligations and the inconsistency of the continued suspension of concessions granted by the DSB to the United States. Brazil states that had the European Communities wanted to follow multilateral rules, it should have requested an Article 21.5 compliance panel, as it did in *EC – Bananas III (Article 21.5 – EC)*.[55]

5.25 Brazil argues that Article 21.5 of the DSU does not specify which Member is to initiate Article 21.5 proceeding. Therefore, in Brazil's point of view, when disagreement exists as to the consistency of the measures taken to comply with the DSB recommendations, any party to a dispute may have recourse to the Article 21.5 proceedings. Brazil asserts that nothing in the DSU precludes an implementing Member from resorting to an Article 21.5 panel review. Brazil further argues that Article 6 of the DSU provides a rule for the development of special terms of reference, which could be applied in those cases where the implementing Member requests a panel to analyse its own measure.[56]

C. CHINA

1. Introduction

5.26 China submits that the disputes raised in this case are derived from loopholes embedded in the DSU. China states that this brings to attention the importance of amending those loopholes in the new round of negotiation. According to China, in absence of any revision of the DSU, it is a challenge for this Panel to find suitable dispute settlement solution according to the current DSU.[57]

2. Opening Panel meetings for observation by the public

5.27 China did not provide a reply on the potential legal constraint that would exclude the Panel from opening the Panel meeting for observation by the public. China however preferred the Panel to

[51] Third party submission of Brazil, paras. 22-24.
[52] Replies by Brazil to Panel questions, question 3.
[53] Third party submission of Brazil, paras. 10 and 11.
[54] See EC's first written submission, para. 1
[55] Third party submission of Brazil, paras. 13 and 14.
[56] Replies by Brazil to Panel questions, question 2 and 5.
[57] Third party submission of China, paras. 1 and 2.

meet the third parties in closed session. It argues that based on Article 18.2 of the DSU, panels do not have the right to unilaterally disclose the third party submissions and oral presentations.[58]

3. The current status of the DSB authorized suspension of concessions

5.28 China submits that under Article 22.8, a DSB authorized suspension of concessions shall not be applied, if one of three of the following conditions has been met:[59]

(a) The measure found to be inconsistent with a covered agreement has been removed;

(b) The Member that must implement the recommendations or rulings provides a solution to the nullification or impairment of benefits;

(c) A mutually satisfactory solution is reached.

5.29 China contends that if a mutually satisfactory solution is reached by the parties on (a) or (b) above, it will fall into condition (c) and then a DSB authorized suspension of concessions shall not be applied. China posits that if there is no mutually satisfactory solution reached by the parties on whether condition (a) and/or (b) above has been met, the parties have to invoke the dispute settlement procedures to let the Panel make such determination. China posits that in case the responding party declares any of the above conditions has been satisfied, there are only two options for the complaining party: (a) to admit the compliance of new measures; or (b) to deny it.[60]

5.30 In China's view, in case the original complaining party denies the compliance of new measures, that is, if no agreement is reached between the parties as to whether the conditions under Article 22.8 of the DSU have been met, under Article 23 of the DSU, the parties shall have recourse to the DSB's determination to avoid unilateral determination.[61]

5.31 China thus considers that there are only two ways to terminate a DSB authorized suspension of concessions: (i) to reach a mutually satisfactory solution; (ii) to get a final determination from the DSB. According to China, this is the case, even when the original complaining party needs a reasonable period of time to evaluate the WTO consistency of the implementation measure.[62]

5.32 China argues that the European Communities' allegation that it has removed the measure at issue in itself could not give the European Communities ground to terminate the authorization of suspension of concessions. China asserts that Article 23 of the DSU lays down the fundamental principle that the dispute settlement system of the WTO is the exclusive means to redress any violation of any provision of the WTO Agreement. It argues that since there is no mutually satisfactory solution between the European Communities and Canada, the DSB authorized suspension of concessions shall be applied until the DSB makes a new determination on the authorization of suspension of concessions. China notes that the suspension of concessions pursuant to a DSB authorization is temporary and conditional, with the condition being that the original responding party fully implements the rulings and recommendations of the DSB. China emphasizes that no party can make a unilateral determination on whether condition (i) and/or (ii) has been met.[63]

5.33 China emphasizes that if this Panel allows the original responding party to terminate a DSB authorized suspension of concessions by introducing an implementing measure, there is a risk that it

[58] Replies by China to Panel questions concerning open hearings, questions 1 and 2.
[59] Third party submission of China, para. 6.
[60] Third party submission of China, paras. 7 and 8.
[61] Replies by China to Panel questions, question 7.
[62] Third party submission of China, para. 9.
[63] Third party submission of China, para. 10 and oral statement of China, paras. 3-4.

could be abused by an original responding party who, instead of bringing its measures into full conformity with the recommendations and rulings of the DSB, may implement legislation which does not cure all the defects in its earlier inconsistent legislation. China argues that if this Panel finds a DSB authorized suspension of concessions to remain in effect after the original responding party introduced an implementing measure, it can help enforcing WTO rules by inducing actual compliance.[64]

5.34 China is of the view that the suspension of concessions has at least two functions: (i) to rebalance the interests among parties; (ii) to force the responding party to bring its measure into compliance with the covered agreement. China posits that if this Panel allows the original responding party to introduce an implementing measure to override the DSB-authorized suspension of concessions, it invalidates the second function of suspension of concessions.[65]

4. Article 21.5 of the DSU and burden of proof

5.35 China states that Article 21.5 of the DSU does not preclude the original responding party from having recourse to the dispute settlement procedures in the event that there is disagreement as to the existence or consistency with a covered agreement of measures taken to comply with the recommendations and rulings. China advances the following reasons for this argument.[66]

5.36 First, according to China, it would be natural and logical only for the original complaining party to initiate an Article 21.5 proceeding. China quotes *Chile – Alcoholic Beverages*[67] and *Canada – Aircraft (Article 21.5 – Brazil)*[68]and argues that the original responding party when adopting measures to implement recommendations and rulings of the DSB shall be presumed to have fulfilled its WTO obligations, and therefore, shall not bear the burden to demonstrate compliance. China notes that this is further justified because the European Communities' implementation measure requires conducting extensive scientific studies and performing a comprehensive risk assessment in a transparent and objective manner. According to China therefore, after the European Communities notifies the DSB of its measure to implement the recommendation and rulings of the DSB, it has fulfilled the procedure obligation under the DSU, and should not be required to bear the burden of proof.[69]

5.37 Secondly, China refers to the practice of treaty interpretation as elucidated in Article 31.3 of the *Vienna Convention on the Law of Treaties* and *Japan – Alcoholic Beverages II*[70], and points out that the statistics of panel proceedings on compliance under Article 21.5 of the DSU show that in most cases, it is the original complaining party that initiates the dispute settlement procedure under Article 21.5 of the DSU. China stresses that the only precedent for an original responding party to initiate the dispute settlement procedure under Article 21.5 of the DSU is in the *EC – Bananas*[71] dispute where the European Communities as an original responding party sought the establishment of a compliance panel under Article 21.5 of the DSU with the hope of preventing the United States from having recourse to Article 22.6 of the DSU directly. China asserts that this subsequent practice in the

[64] Third party submission of China, paras. 11 and 12.
[65] Replies by China to Panel questions, question 3.
[66] Third party submission of China, para. 15.
[67] Third party submission of China, para. 17.
[68] Third party submission of China, para. 18.
[69] Third party submission of China, paras. 19 and 20.
[70] See Appellate Body Report on *Japan – Alcoholic Beverages II* (WT/DS8/AB/R, WT/DS10/AB/R, WT/DS11/AB/R) p. 13
[71] *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Article 21.5 by the European Communities*, Report by the Panel (WT/DS27/RW/EEC), 12 April 1999 – report never adopted.

application of Article 21.5 of the DSU establishes the agreement of the parties regarding their interpretation that the original complaining party should initiate the Article 21.5 proceeding.[72]

5.38 Thirdly, China argues, the balance of hardship to initiate an Article 21.5 proceeding does not favour the original complaining party. China believes that the original complaining party will suffer no cognizable harm if it initiates an Article 21.5 proceeding, because the DSB authorized suspension of concessions is still in effect. China asserts that it is not proper to let the European Communities initiate an Article 21.5 proceeding simply because the original complaining party is reluctant or has no incentive to do so.[73]

5.39 China stresses that it should be presumed that when the original responding party introduces an implementation measure, it has fulfilled its WTO obligation, and it should be the duty of the original complaining party to demonstrate that the implementation measure is still inconsistent with the covered agreement. China believes if this Panel rules that the European Communities, as an original responding party, should initiate an Article 21.5 proceeding, it will unduly shift the heavy burden on the shoulders of the European Communities to establish the compliance, which is against the nature and logic of the Article 21.5 proceeding.[74]

5.40 China contends that it is usually the case that the responding party has more information on its implementation measure, therefore it is better positioned to demonstrate the WTO consistency of the measure. However, according to China, the nature and logic of the Article 21.5 proceedings stands against this approach. China stresses that subsequent practice in the application of Article 21.5 confirms this conclusion. China is therefore of the opinion that the original complaining party should bear the burden to institute the Article 21.5 proceeding.[75]

5.41 China continues that the unique part of this case is that the original complaining party has a DSB authorized suspension of concessions. According to China, in addition to the function of inducing compliance, this authorized suspension of concessions can rebalance the trading relationship between the complaining and the original responding party in order to restore the economic equilibrium embodied in the original WTO deal. China submits that if after the original panel proceeding, an original complaining party finds that the original responding party does not implement the recommendations and rulings of the DSB, it has incentive to initiate an Article 21.5 proceeding, because it still suffers from a WTO inconsistent measure. However, in this case, China submits that due to the rebalance by the authorized suspension of concessions, the original complaining party may not have the same incentive, therefore it may be necessary to set up a time limit for it to initiate an Article 21.5 proceeding.[76]

5.42 China argues that the proceedings under Article 21.5 of the DSU shall be initiated in a reasonable period of time. China points out that it is in line with the good faith requirement established by Article 26 of the *Vienna Convention on the Law of Treaties* and it is also consistent with the requirement of "prompt settlement of situations" in Article 3.3 and the "temporary nature" of the retaliation system of the DSU.[77]

5.43 China stresses that it wants to bring to the Panel's attention that both Article 22.8 and Article 21.5 of the DSU do not preclude this Panel from setting a time limit to initiate the dispute settlement proceedings. If this Panel holds that it should be the original complaining party to invoke

[72] Third party submission of China, paras. 21-24.
[73] Third party submission of China, para. 25.
[74] Third party submission of China, para. 26.
[75] Third party submission of China, paras. 27 and 28.
[76] Third party submission of China, para. 29.
[77] Third party submission of China, para. 31.

Article 21.5 of the DSU, to facilitate the implementation of this recommendation and ruling, it may be necessary to set up a time limit for the original complaining party to initiate an Article 21.5 proceeding.[78]

5. Article 23.2 of the DSU

5.44 China argues that to establish a violation of Article 23.2 (a), the Panel shall first assess whether the act of "determination" is made "in such cases", where a Member seeks the redress of a WTO violation.[79]

5.45 China analyses the different interpretations of the term "seek the redress of violation" in *US – Section 301 Trade Act*,[80] in *US – Certain EC Products*"[81] and in *European Communities – Measures Affecting Trade in Commercial Vessels*,[82] and states that the term "seek the redress of a violation" should be read broadly to cover any act as long as it seeks to obtain unilateral results that can be achieved through means other than recourse to the DSU. China states that in this case, the original complaining party's continued suspension of concessions could be considered as a measure seeking the redress of a WTO violation, if it had a chance to challenge the European Communities' WTO violation but held back, allowing the DSB authorized suspension of concessions to apply continuously.[83]

5.46 China argues that after the European Communities provided notice of the Directive to the DSB in October 2003, the original complaining party cast doubt on the WTO consistency of this European Communities' implementation measure. Since then the complaining party has had a reasonable period of time to review the European Communities measure and to initiate Article 21.5 proceedings. China argues that it is the lack of action under Article 21.5 of the DSU by the original complaining party, rather than the DSB authorized suspension of concessions itself, that may be considered as seeking the redress of a violation.[84]

5.47 With respect to the meaning of the term "determination", China refers to the panel in *US – Section 301 Trade Act*[85] and argues that the term "determination" in Article 23.2(a) of the DSU needs to be read broadly and it does not require that a measure clearly sets out in its text that a WTO violation has occurred. China argues that such a determination may be inferred from actions. According to China, the longer the time period in which the original complaining party took no action under Article 21.5 of the DSU, the greater the firmness or immutability it made such a determination.[86]

5.48 China argues that where there is no official determination, the Panel has to find a way to evaluate the firmness and immutability of the alleged determination. China notes that before the decision becomes final, there could be a gradual change process in which a time lapse can be a parameter. According to China, in the post-retaliation phase, the clock starts ticking when the original responding party introduces a new measure. China argues that the amount of time needed to constitute a final determination by the original complaining party under Article 23 of the DSU depends on several factors, including but not limited to (1) the complexity of the compliance measure;

[78] Third party submission of China, para. 32.
[79] Third party submission of China, para. 35.
[80] See Panel Report on *US – Section 301 Trade Act*, para. 7.50, footnote 657.
[81] See Panel Report on *US – Certain EC Products*, paras. 6.22 and 6.23.
[82] See Panel Report on *EC – Commercial Vessels*, WT/DS301/R, para. 7.196
[83] Third party submission of China, paras. 36-39.
[84] Third party submission of China, para. 40.
[85] See Panel Report on *US – Section 301 Trade Act*, para. 7.50, footnote 657.
[86] Third party submission of China, paras. 41 and 42.

(2) sufficiency of information related to the compliance measure; and (3) the ability of the original complaining party to evaluate such new measure.[87]

D. INDIA

1. Introduction

5.49 India submits that it takes no position on the respective assertions of the parties in this dispute. India notes however that the treaty text is not clear on the respective rights and obligations of the party taking a compliance measure and the party applying sanctions. India contends that this is evidenced by the fact that this is one of the major issues on which the WTO Membership is currently engaged in negotiation with a view to improve or clarify the legal text. India states that it has views on how the lacunae in the DSU on this issue can be improved or clarified, but that is a matter for the Membership to decide through future negotiations.[88]

2. Opening Panel meetings for observation by the public

5.50 India submits that the issue of external transparency is being discussed in the ongoing negotiations in the Special Session of the Dispute Settlement Body. India states that the negotiations have not yet been completed, and there is no consensus on whether and which form of external transparency is acceptable to the WTO Members. Until that happens, India believes that the Panel proceedings have to be in closed session,[89] and its deliberations have to remain confidential[90] as provided in the DSU.[91]

5.51 India posits that it is not a function of a panel to respond to any requests from the parties that do not assist in resolution of the matter before it, and which are not in the terms of reference of the panel.[92]

5.52 India contends that the possibility of a panel to decide to deviate from the Working Procedures in Appendix 3 has been provided with a view to have panel procedures with sufficient flexibilities so as to ensure high-quality panel reports[93]. In India's view, deviation from the Working Procedures, therefore, should meet this qualitative objective. India quotes Article 12.1 of the DSU and the Panel in *India – Patents (US)*[94] *and argues that although p*anels are given some discretion in establishing their own working procedures, they do not have the discretion to modify the substantive provisions of the DSU. India argues that the confidentiality requirements for panel proceedings are a substantive provision of the DSU, and the Panel cannot use its discretion to modify them in order to cater to a request by the parties on a matter that does not serve to improve the quality of the Panel's Report.[95]

5.53 India argues that Article VII of the Rules of Conduct[96] requires each "covered person" to maintain the confidentiality of dispute settlement deliberations and proceedings at all times. India

[87] Replies by China to Panel questions, question 1.
[88] Oral statement by India, para. 3.
[89] Paragraph 2 of the Working Procedures in Appendix 3 of the DSU
[90] Paragraph 3 of the Working Procedures in Appendix 3 of the DSU
[91] Replies by India to Panel questions concerning open hearings, question 1.
[92] Oral statement of India, para. 5.
[93] Article 12.2, DSU
[94] *India – Patent Protection for Pharmaceutical and Agricultural Chemical Products – Complaint by the United States*, Panel Report, WT/DS50/R.
[95] Oral statement of India, para. 6.
[96] Rules of conduct for the understanding on rules and procedures governing the settlement of disputes adopted by the DSB on 3 December 1996 (WT/DSB/RC/1).

questions how the Panel is going to ensure that these requirements are met after opening the proceedings to the public for observation.[97]

5.54 India submits that the decision of the Panel to open its proceedings to the public necessarily involves some issues on which consultation and decisions with WTO members, and not just the parties and third parties, would have been necessary. For example, India questions how the Panel, at its own level, addressed issues relating to the implications on the functioning of the WTO Secretariat, budgetary implications and implications relating to the use of the official languages of the WTO, for which rules and practices have been established by other bodies of the WTO. India also questions how the Panel could take a view on the additional costs arising out of the opening up of the proceedings to public without the Budget Committee having considered the matter.[98]

5.55 According to India, the WTO is a Member driven organization and it is solely for the WTO Members to decide whether or not to change the WTO rules and open up panel proceedings to the public; a Panel cannot take upon itself that function, even at the request of parties to the dispute.[99]

5.56 India posits that the meeting of the Panel's session with the third parties should be in closed session as required under paragraph 2 of the Working Procedures contained in Appendix 3 of the DSU.[100]

E. MEXICO

1. Introduction

5.57 Mexico submits that the systemic implications of this dispute are of great importance in terms of the functioning of the DSU and in particular of defining a way of proceeding when there is an authorization to suspend benefits and then further disagreement as to whether or not the DSB's recommendations and rulings have been implemented. In Mexico's view, the most important issue in this case is whether the adoption of implementation measures "require" immediate termination of retaliatory measures and if not, who should require termination and how. According to Mexico, the role of the Panel in this case is to give precise answers to these questions and to ensure that they fulfil not only the letter of the DSU, but also the objectives of security, predictability and prompt settlement of the dispute.[101]

2. Opening Panel meetings for observation by the public

5.58 Mexico disagreed with the opening of the panel meetings to the public on the grounds that panel meetings constitute panel "deliberations" and as such should be confidential, as per Article 14.1 DSU. Mexico also argues that transparency is a sensitive issue that is currently under discussion in the negotiations to amend the DSU thus to force one or another negotiating position by taking such a decision is inappropriate. Mexico argues that the DSU rules require that the meetings be confidential and therefore, bilateral agreement among parties is not suffice to bend the rules. In its view, therefore, the decision of the two parties should only prevail to the extent that it does not affect the right of other DSB Members including third parties. Mexico contends that if the Panel is to depart from the Working Procedures of Appendix 3, the Panel must do so with caution as such deviation is meant to grant flexibility so as to ensure high quality panel reports, as seen in Article 12.2 DSU.[102]

[97] Oral statement of India, para. 7.
[98] Oral statement of India, para. 8.
[99] Oral statement of India, para. 9.
[100] Replies by India to Panel questions concerning open hearings, question 2.
[101] Replies by Mexico to Panel questions concerning open hearings, question 1, paras. 2, 3 and 9.
[102] Oral statement of Mexico, para. 2; Replies by Mexico to Panel questions, paras. 3 and 9.

5.59 Mexico emphasizes that public hearings are a cross-cutting issue that should be addressed in all the discussions conducted in the WTO, and should not be imposed by a panel at the request of three Members. Mexico regrets that the decision will set a precedent that may affect the outcome of the negotiations and which will in all likelihood end up complicating the preparation of working procedures of future panels.[103]

5.60 Mexico notes that if the Panel is to open the meetings to the public observation, as a policy perspective, it poses systemic questions as to the necessity to open negotiation meetings and ordinary sessions of the WTO bodies to the public.[104] Mexico suggests that third party sessions follow the established WTO practice of being closed session.[105]

3. Whether the DSB authorization remains in effect

5.61 According to Mexico, the Panel should reject the argument that a simple unilateral notification is enough to reduce multilateral effort to nothing. Mexico contends that the Panel should bear in mind the lengthy procedure and high political costs to Members of obtaining a multilateral authorization to suspend concessions.[106]

5.62 Mexico stresses that it can not allow a dispute settlement system to deprive all effect of the authority to suspend benefits when a Member has failed to implement the DSB's recommendations and rulings within the reasonable period. In its view, in such a case, if the parties fail to agree, the matter must be resolved by a multilateral decision.[107]

5.63 Mexico argues in its reply to the questions posed by the European Communities that a DSB decision may be affected only by another DSB decision taking away the effect of the first decision.[108]

4. Article 21.5 of the DSU

5.64 Mexico claims that Article 21.5 DSU affords the most suitable procedure for resolving this dispute and it could be initiated by any party. Mexico however submits that the dispute could be dealt with either by an ordinary panel, or through arbitration under Article 25 DSU or indeed by any of the proceedings provided for in Article 5 DSU. Mexico however points out that it takes a constructive approach and good will by the parties to make Article 21.5 DSU function and be able to resolve any disagreements.[109]

F. NEW ZEALAND

1. Introduction

5.65 New Zealand submits that this case raises important issues about the integrity and effectiveness of the WTO dispute settlement system, as it is principally about issues of compliance and the proper interpretation and application of the rules of the DSU as they relate to the post-retaliation phase. In New Zealand's view, the case taken by the European Communities is for all intents and purposes a compliance case and is thus akin to an Article 21.5 case. According to New Zealand, the same determinations are required to resolve the case at hand, as would be required had it

[103] Oral statement of Mexico, para. 3.
[104] Replies by Mexico to Panel questions concerning open hearings, question 1, para. 7.
[105] Replies by Mexico to Panel questions concerning open hearings, question 2.
[106] Oral statement of Mexico, para. 5.
[107] Oral statement of Mexico, para. 4.
[108] Replies by Mexico to questions from the European Communities, question 4.
[109] Oral statement of Mexico, para. 6.

been commenced under Article 21.5. In New Zealand's view, the Panel's terms of reference[110] are sufficiently broad to encompass this question and in doing so, the Panel should focus on actual compliance and not presumed compliance.[111]

2. Opening Panel meetings for observation by the public

5.66 According to New Zealand, there are no legal constraints that would prevent the Panel from opening the Panel hearings to the public. New Zealand quotes Article 12.1 which allows panels to follow Working Procedures unless the panel decides otherwise after consulting the parties. New Zealand argues that while Appendix 3 provides for closed session hearings, the Working Procedure can be amended on the consent of the panel and the parties. New Zealand further stipulates that the reference in Article 14.1 of the DSU to panel deliberations being confidential refers to the internal deliberations of the panel, not the hearings with the parties. New Zealand submits that this is in line with the practice of other international tribunals which have open hearings but whose deliberations are nonetheless confidential. According to New Zealand, Article 18.2 of the DSU allows parties to waive confidentiality. New Zealand did not object to its third party hearings being public.[112]

3. Whether the DSB authorization remains in effect

5.67 New Zealand submits that there is no obligation on the United States to take an Article 21.5 case, and that in the absence of a determination of compliance from the DSB, the DSB's authorization of suspension of concessions remains valid.[113]

5.68 New Zealand argues that underlying the European Communities' arguments is the assumption that it should benefit in these circumstances from a presumption of compliance on the basis of the principle of good faith.[114] New Zealand however does not agree that the said principle applies in the current circumstances, to require the United States to cease the suspension of concessions and commence Article 21.5 proceedings simply because the European Communities has notified that it now considers itself to be in compliance. According to New Zealand, a presumption of good faith cannot override an explicit multilateral authorization from the DSB to impose a retaliatory suspension of concessions.[115]

5.69 In New Zealand's view, the cases cited by the European Communities in support of the application of a presumption of compliance involve measures that were implemented within the reasonable period of time and where there was no authorization to suspend concessions, which is not the situation at present. New Zealand opines that even if it can be said that a presumption of compliance operates in the pre-retaliation period while the reasonable period of time is still pending, in the current circumstances any presumed compliance on the part of the European Communities has

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[110] WT/DS320/6 of 14 January 2005 and WT/DS/320/7. The Request for the Establishment of a Panel by the European Communities states, *inter alia*, that:

The United States has acted inconsistently with Article 22.8 of the DSU by failing to apply the suspension of concessions or other obligations only until such time as the measure found to be inconsistent with a covered agreement has been removed, or the implementing Member has provided a solution to the nullification or impairment of benefits previously caused to the United States. (emphasis added).

[111] Third party submission of New Zealand, paras. 1.06 and 2.19.

[112] Replies by New Zealand to Panel questions concerning open hearings, questions 1 and 2.

[113] Third party submission of New Zealand, para. 2.09.

[114] The European Communities sets out its arguments on the 'presumption of compliance' in paras. 81-94 of its First Written Submission in addressing its argument that the United States is in violation of Article 23.1 read together with Articles 22.8 and 3.7 of the DSU.

[115] Third party submission of New Zealand, paras. 2.10 and 2.11.

given way to the actual compliance of the suspension of concessions which has been duly authorized by the DSB.[116]

4. Articles 21.5, 22.8 and 23 of the DSU

5.70 New Zealand argues that while it would be open to the respondent to initiate compliance review under Article 21.5, the argument that Article 23 read with Articles 21.5, 22.8 and 3.7 imposes a requirement to do so cannot be sustained. New Zealand insists that Article 21.5 merely states that the disagreement shall be dealt with through recourse to the dispute settlement procedures, but does not place any particular onus on any one to commence proceedings.[117]

5.71 New Zealand contends that Article 23 is the framework provision setting up the requirement to have recourse to dispute settlement when seeking redress of a violation of obligations. New Zealand however argues that Article 23 does not address the specific situation in this case, where the United States has had recourse to dispute settlement in accordance with this Article and has taken all the steps there identified. New Zealand submits that Article 23 does not impose an obligation on the United States to cease the application of the suspension of concessions or to take a compliance review case where it does not accept that the measure has been removed. Nor does it do so when "read together" with Articles 3.7 and 22.8. New Zealand argues that it cannot see how these provisions can be read to displace the specific authorization under Article 22.6, which has never been revoked.[118]

5.72 New Zealand posits that if the Panel were to adopt the European Communities' approach, it would give rise to a situation where an implementing Member could continually impose successive rounds of litigation at will, by a mere assertion of compliance. In New Zealand's view this could render useless the mechanism of suspension of concessions. According to New Zealand, this approach is inconsistent with the aims and objectives of the dispute settlement system given the fundamental importance of suspension of concessions as the 'last resort' of the dispute settlement system, as per Article 3.7 DSU.[119]

5.73 New Zealand points out that the suspension of concessions may not be maintained indefinitely in circumstances where the violation has been addressed as stipulated in Article 22.8 of the DSU. According to New Zealand, if the respondent maintains the suspension notwithstanding, then there is a "disagreement as to the existence or consistency ... of measures taken to comply" with the recommendations within the terms of Article 21.5. As a consequence it is open to the party concerned about this to have recourse to the dispute settlement procedures to resolve the disagreement.[120]

5.74 New Zealand notes that this does not mean however, that sanctions may go on forever even in cases where there is full compliance but the new measure has not been challenged. New Zealand considers that if a measure taken to comply does indeed remove the inconsistency with the recommendations and rulings of the DSB, the suspension of concessions should be ceased. In its view, the justification for continuing to suspend concessions would be the combination of the continuing DSB authorization and the absence of any agreement that the original respondent has brought its measures into compliance.[121]

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[116] Third party submission of New Zealand, para. 2.12.
[117] Third party submission of New Zealand, para2.14.
[118] Third party submission of New Zealand, paras. 2.14-2.16.
[119] Third party submission of New Zealand, para. 2.17.
[120] Third party submission of New Zealand, para. 2.18.
[121] Replies by New Zealand to questions from the European Communities, questions 4 and 5.

5.75 In New Zealand's view, it is possible for an implementing Member to initiate an Article 21.5 proceeding in any case "where there is disagreement as to the existence or consistency with a covered agreement of measures taken to comply with the recommendations and rulings" of the DSB.[122]

5.76 New Zealand states that Article 21.5 does not specify the procedures to be applied, beyond stipulating that the matter be referred to the original panel and that there be an accelerated timeframe for circulation of the report. It further contends that the consequence is that it is up to the Panel to establish the Panel procedures in accordance with Article 12 of the DSU.[123]

5.77 New Zealand submits that there is no textual basis in the DSU for concluding that an original complainant that maintains a multilaterally authorized suspension of concessions after notification of a compliance measure by the original respondent and does not initiate Article 21.5 proceedings, is in violation of its obligations under the DSU.[124]

5. Burden of proof

5.78 New Zealand submits that the European Communities bears the burden of proving a prima facie inconsistency with Article 22.8 of the DSU. New Zealand refers to the Appellate Body decision in *US – Wool Shirts and Blouses*[125], and contends that the European Communities must adduce evidence sufficient to raise a presumption that the suspension of concessions continues to apply and that: (a) it has removed the measure found to be inconsistent with the *SPS Agreement*; or (b) it has provided a solution to the nullification or impairment of benefits; or (c) a mutually satisfactory solution has been reached. The European Communities does not argue (b), and (c) is clearly not the case, but it instead relies on (a).[126]

5.79 New Zealand submits that the European Communities has not demonstrated in its first written submission that it has removed the inconsistent measure. According to New Zealand, 'removal' of an inconsistent measure for the purposes of Article 22.8 of the DSU may be interpreted as compliance with the recommendations and rulings of the DSB. 'Removal' of the measure in this case could involve the removal of the import prohibition and/or establishing a justification for the prohibition through a risk assessment consistent with the *SPS Agreement*, taking into account the particular requirements which the Panel and Appellate Body reports identified.[127]

6. Article 5.7 of the *SPS Agreement*

5.80 New Zealand posits that as the Member seeking to have recourse to Article 5.7, the burden of proof rests on the European Communities to demonstrate that the four requirements of that provision have been met.[128] New Zealand is of the view that while not explicitly stated by the European Communities, the provisional import ban on the five hormones other than oestradiol-17β appears to be an attempt to bring those measures within the qualified exemption provided of Article 5.7 of the *SPS Agreement*. According to New Zealand, as seen in *Japan – Agricultural Products II*[129], the European Communities must demonstrate that: (a) its measure was imposed in a situation where

[122] Replies by New Zealand to questions from the European Communities, question 6.
[123] Replies by New Zealand to Panel questions, question 2.
[124] Replies by New Zealand to Panel questions, question 5.
[125] *United States – Measure Affecting Imports of Woven Wool Shirts and Blouses from India (US – Wool Shirts and Blouses)*, WT/DS33/AB/R, 25 April 1997, p. 14.
[126] Third party submission of New Zealand, paras. 2.21-2.22
[127] Third party submission of New Zealand, para. 2.26.
[128] The Panel in *Japan – Measures Affecting the Importation of Apples* (*Japan – Apples*), WT/DS245/R, 15 July 2003, discussed at para. 8.212 the burden of proof under Article 5.7.
[129] Appellate Body Report on *Japan – Measures Affecting Agricultural Products (Japan – Agricultural Products II)*, WT/DS76/AB/R, 22 February 1999, para. 89.

'relevant scientific evidence is insufficient'; and that (b) its measure was adopted "on the basis of available pertinent information, including that from relevant international organisations as well as from sanitary or phytosanitary measures applied by other Members."[130]

5.81 New Zealand claims that pursuant to the second sentence of Article 5.7, the European Communities may not maintain its measure unless it also: (a) 'seek[s] to obtain the additional information necessary for a more objective assessment of risk'; and (b) 'review[s] the measure accordingly within a reasonable period of time'. New Zealand posits further that the Appellate Body added that "[w]herever *one* of these four requirements is not met, the measure at issue is inconsistent with Article 5.7."[131] New Zealand argues that the European Communities states that its provisional ban on five of the six hormones was adopted "on the basis of the available but still incomplete data".[132] However, according to New Zealand, the European Communities is not required under Article 5.7 to show that the relevant scientific evidence was 'incomplete', but rather that it was 'insufficient'. New Zealand quotes the Appellate Body in the *Japan – Apples* case, which analysed the meaning of this expression that:[133]

> " '[R]elevant scientific evidence' will be 'insufficient' within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*."[134]

5.82 New Zealand is of the opinion that the European Communities in its first written submission does not establish a prima facie case that relevant scientific evidence does not allow an adequate risk assessment to be carried out. New Zealand argues that the European Communities fails in its first written submission to explain how the current state of scientific knowledge has prevented it from conducting an adequate risk assessment with respect to the five hormones. According to New Zealand, this is even more difficult to understand when the same measure, an import ban, which the European Communities previously maintained was based on sufficient scientific evidence to be definitive, is now held out as a merely 'provisional' measure.[135]

5.83 New Zealand submits that on the other hand, the respondent in its first written submission shows that a considerable body of relevant scientific evidence exists as to the use of hormones for growth promotion purposes.[136] New Zealand argues that the United States points out that the hormones at issue have been "intensively studied over the last twenty-five years"[137] and that the five particular hormones subject to the provisional ban have been "studied in greater detail in the intervening period (since the original *Hormones* case)".[138] According to New Zealand, the inference to be taken is that the relevant scientific evidence is both quantitatively and qualitatively sufficient to have enabled the European Communities to conduct an adequate risk assessment, and avoid the need for recourse to provisional measures.[139]

5.84 New Zealand further opines that even if the Panel were to accept that there was insufficient scientific evidence for the European Communities to conduct an adequate risk assessment, the European Communities must also show that its new measure was adopted 'on the basis of available

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[130] Third party submission of New Zealand, paras. 2.28 and 2.29.
[131] Appellate Body Report on *Japan – Agricultural Products II*, para. 89. Emphasis original.
[132] EC's first written submission, para. 145.
[133] Third party submission of New Zealand, paras. 2.30-2.32.
[134] Appellate Body Report on *Japan – Apples*, para. 179.
[135] Third party submission of New Zealand, para. 2.34.
[136] See US's first written submission at paras. 55-91.
[137] US's first written submission, para. 122.
[138] US's first written submission, para. 123.
[139] Third party submission of New Zealand, para. 2.35.

pertinent information'. New Zealand stresses that in order to satisfy the burden of proof, the European Communities must present the 'available pertinent information' it evaluated and the factors that led it to conclude that a provisional import ban on the five hormones could reasonably be based on this information. New Zealand states that the European Communities failed in its first written submission to establish any connection between its provisional import ban and: (a) the available pertinent information; (b) information from relevant international organisations; and (c) information from sanitary or phytosanitary measures applied by other Members.[140]

5.85 According to New Zealand, by contrast, the United States claims that a large body of 'available pertinent information'[141] indicates that proper use of the hormones in question poses no risk to consumers.[142]

5.86 New Zealand submits that under the third limb of Article 5.7, in a situation where the relevant scientific evidence is insufficient to conduct an adequate risk assessment, the European Communities is required to 'seek to obtain the additional information necessary for a more objective assessment of risk'. New Zealand contends that the European Communities implies that this requirement is reflected in Directive 2003/74/EC, which obliges the Commission "to seek more complete scientific information from any source which could shed light and clarify gaps in the present state of knowledge on [the hormones]."[143] New Zealand however submits that the European Communities offers no evidence in its first written submission to explain how the Commission is fulfilling this obligation.[144]

5.87 New Zealand further opines that the final element of Article 5.7 requires the European Communities to 'review' its provisional measures 'within a reasonable period of time'. New Zealand notes that while a competent WTO body has yet to analyse what constitutes a 'reasonable period of time,' Directive 2003/74/EC has been in force for nearly two years, but the European Communities makes no suggestion in its first written submission that a review of the provisional import ban is contemplated at all, let alone within a 'reasonable period of time'. New Zealand submits that the European Communities has failed to discharge its burden of proof with respect to the four elements of Article 5.7 in its first written submissions.[145]

7. Article 5.1 of the *SPS Agreement*

5.88 New Zealand alleges that the European Communities has not demonstrated in its first written submission that its new measures meet the requirements of Article 5.1 *SPS Agreement*. New Zealand contends that the Appellate Body in *EC – Hormones* established that the obligation in Article 5.1 contains two elements: (a) an assessment of risks; and (b) that Members ensure that their SPS measures are "based on" such an assessment. New Zealand argues that concerning the first element of Article 5.1, paragraph 4 of Annex A of the *SPS Agreement* sets out the definition of a "risk assessment". New Zealand quotes the Appellate Body[146] that recalled Article 5.2 of the *SPS Agreement*, which provides an indicative list of factors that must be taken into account in a risk assessment.[147]

5.89 New Zealand further argues that the panel in the *Japan – Apples* case summarised its consideration of the elements of Article 5.1 by recalling that a risk assessment would also involve an evaluation of whether the risk assessment was 'as appropriate to the circumstances', and whether it

[140] Third party submission of New Zealand, para. 2.36.
[141] See US's first written submission, paras. 127-128.
[142] Third party submission of New Zealand, para. 2.37.
[143] EC's first written submission, para. 145.
[144] Third party submission of New Zealand, para. 2.38
[145] Third party submission of New Zealand, paras. 2.38 and 2.39.
[146] Appellate Body Report on *EC – Hormones*, para. 187.
[147] Third party submission of New Zealand, paras. 2.42-2.44.

took into account 'risk assessment techniques developed by the relevant international organizations'.[148] New Zealand posits that the panel in that case added that these two factors would "pervade the entire assessment of the risk".[149]

5.90 New Zealand stresses that while the European Communities claims to have conducted "a comprehensive risk assessment" since the Appellate Body decision in 1998[150], it devotes only three paragraphs of its first written submission to attempting to establish what constitutes a valid risk assessment for the purposes of Article 5.1. New Zealand submits that the European Communities notes that it has initiated 17 scientific studies and research projects, but enters into no discussion of the substance, conduct or conclusions of these studies.[151] According to New Zealand, the European Communities observes that it addressed specific requests for scientific data to several countries and published an open call for relevant and recent scientific data and information from any interested party, but makes no comment on the information received.[152]

5.91 New Zealand further opines that in its first written submission, the European Communities simply refers to the SCVPH Opinions and presents a three-paragraph excerpt from Directive 2003/74/EC[153] which provide, on the face of it, a rather limited and constrained justification for the European Communities' import ban. Further, New Zealand posits that the European Communities articulates no clear link between "excess intake of hormone residues" (which is not defined in relation to use as a growth-promoting hormone) and "a risk" that has been identified.[154]

5.92 In New Zealand's view, the European Communities' recital and its bare conclusion fall well short of demonstrating that the European Communities has met the threshold required under the *SPS Agreement* for the existence of a valid risk assessment. New Zealand notes that in particular, the European Communities fails in its first written submission to adduce sufficient evidence that its risk assessment: (a) adequately identifies any adverse effects on human health arising from the presence of the hormones in question when used as growth promoters in meat;[155] (b) evaluates the potential or possibility of occurrence of such adverse effects;[156] (c) is 'as appropriate to the circumstances';[157] (d) takes into account risk assessment techniques developed by the relevant international organisations;[158] and (e) takes into account the available scientific evidence as matters specified in Article 5.2 of the *SPS Agreement*.[159]

5.93 New Zealand argues that none of these criteria is optional in the performance of a risk assessment, and therefore the European Communities is required to demonstrate that all of them have been satisfied in the development of its opinions. New Zealand submits that the European Communities has failed to adduce sufficient evidence to discharge this burden.[160]

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[148] Panel Report on *Japan – Apples*, para. 8.236.
[149] Panel Report on *Japan – Apples*, para. 8.237.
[150] EC's first written submission, para. 142.
[151] EC's first written submission, para. 142.
[152] Third party submission of New Zealand, para. 2.48.
[153] EC's first written submission, para. 144.
[154] Third party submission of New Zealand, para. 2.49.
[155] *SPS Agreement*, Annex A, paragraph 4. Extrapolated from the Panel Report in *EC – Hormones*, para. 8.101, as considered in the Appellate Body Report at paras. 183-184.
[156] *SPS Agreement*, Annex A, paragraph 4. Extrapolated from the Panel Report in *EC – Hormones*, para. 8.101, as considered and modified in the Appellate Body Report at paras. 183-184.
[157] *SPS Agreement*, Article 5.1.
[158] *SPS Agreement*, Article 5.1.
[159] Third party submission of New Zealand, para. 2.51.
[160] Third party submission of New Zealand, para. 2.52.

5.94 New Zealand contends that in contrast, the United States outlines some of the scientific evidence that exists on the use of growth-promoting hormones[161], and evokes long-standing practice on the proper assessment of risks related to veterinary drug residues.[162] According to New Zealand, this casts doubt on both the process and the substance of the European Communities' risk assessment.[163]

5.95 New Zealand states that in the event that the Panel decides that the European Communities' opinions constitute a valid risk assessment for the purposes of Article 5.1, the European Communities is also required to demonstrate that the measures in question are 'based on' a risk assessment. According to New Zealand, the Appellate Body analysed this relationship in *EC – Hormones*[164], and states that the term 'based on' required a certain objective relationship between the risk assessment and the measure in question.[165]

5.96 New Zealand argues that the European Communities does not attempt to explain in what way or to what extent its new measures are considered to be 'in accordance' with the scientific conclusions of the SCVPH. New Zealand further stipulates that the European Communities offers no basis at all for concluding that its risk assessment 'reasonably supports' its new measures. New Zealand argues that in this case, the European Communities bears the burden of establishing that its risk assessment 'sufficiently warrants' the new measures it adopted. In New Zealand's view it was not open to the European Communities to leave the existence of a 'rational relationship' to be inferred from a brief summary of the conclusions of the European Communities' opinions.[166]

G. NORWAY

1. Opening Panel meetings for observation by the public

5.97 Norway considers that Article 12.1 of the DSU gives the Panel the discretion to follow other working procedures than the ones provided in Appendix 3 after consulting the parties. It sees no legal constraints in granting the request to the parties to open the hearings to the public. Norway also agrees to have the third party session of the hearing open to the public.[167]

2. Whether the DSB authorization remains in effect

5.98 Norway considers that the right to apply the suspension of concessions pursuant to a DBS authorization is temporary and conditional. According to Norway, the application of the right rests on two basic conditions. First; that there be an authorization pursuant to Article 22.6 DSU and that the conditions set out in Article 22.6 DSU and 22.7 DSU, are respected and secondly, that the temporal condition of Article 22.8 is met.[168]

5.99 Norway opines that the temporal condition in Article 22.8 has three alternative elements: (a) the measure found to be inconsistent with a covered agreement has been removed; or (b) the Member that must implement recommendations or rulings provides a solution to the nullification or impairment of benefits; or (c) a mutually satisfactory solution is reached.[169]

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[161] See, for example, US's first written submission, paras. 55-91.
[162] US's first written submission, para. 136.
[163] Third party submission of New Zealand, para. 2.53.
[164] Appellate Body Report on *EC – Hormones*, para. 193.
[165] Third party submission of New Zealand, para. 2.55.
[166] Third party submission of New Zealand, para. 2.58.
[167] Replies by Norway to Panel questions concerning open hearings, question 1 and 2.
[168] Replies by Norway to questions from the European Communities, questions 3, 4 and 5, para. 2.
[169] Replies by Norway to questions from the European Communities, questions 3, 4 and 5, para. 3.

5.100 Norway contends that the common concept in all the three elements is that continued suspension is related to continued non-compliance or lack of any other mutually satisfactory solution to the inconsistency. According to Norway therefore , the temporal condition is intrinsically linked to the substance of compliance. Norway posits that out of the three elements, the third one, "a mutually satisfactory solution", can in principle be achieved at any point in time and once achieved, would resolve the matter and no suspension may continue. Norway adds that this is even so if the original measure found to be inconsistent with a covered agreement is still in place.[170]

5.101 Norway considers that the first two elements are in reference to compliance, which can be achieved through the removal of the original measure or through another solution to the nullification or impairment of benefits, and the second element is the normal situation where one measure is replaced by another measure.[171]

5.102 Norway submits that once compliance is achieved, be it through a simple revocation of the inconsistent measure or its replacement with another measure that ensures compliance, the right to suspend obligations automatically lapses. Norway is of the view that similarly, once compliance has been established by a panel pursuant to Article 21.5 of the DSU, the previous authorization lapses *ipso facto* once the report is adopted, without there being a need for the DSB to revoke it formally as the temporal condition no longer exists.[172]

5.103 Norway contends that once a measure taken to comply is notified by the original respondent, the question arises whether this amounts to full compliance or not. Norway submits that if the original complainant considers that the measure taken to comply falls short of what is required by the adopted rulings and recommendations, then the obligation to refer a "compliance dispute" to a panel according to Article 21.5 is incumbent upon them.[173]

3. Article 21.5 of the DSU

5.104 Norway argues that the situation addressed by Article 21.5 DSU occurs when the original respondent claims to have complied with the recommendation and ruling of the DSB, but the original complainant disagrees. According to Norway, Article 21.5 is competent both where the parties disagree as to the very existence of measures taken to comply, and where they disagree as to whether the measures taken to comply actually achieve compliance. Norway is of the view that the case at hand is typical in this respect, and falls squarely within the ambit of Article 21.5. Norway notes that neither Article 22.8 nor Article 21.5 sets forth time lines in this respect.[174]

5.105 According to Norway, the original complainant must be accorded a certain amount of time to assess the measure before going to a compliance panel. Norway posits that the length of time needed will vary from case to case, and it is hard to set a fixed dead-line. In Norway's view, the DSU does not include such a fixed dead-line, however, this does not mean that the original complainant can refuse to take action according to Article 21.5 within a reasonable time. Norway thus contends that in order to avoid such unreasonable delay, Article 21.5 allows the original respondent to have recourse to a compliance panel.[175]

5.106 Norway contends that the obligation to refer a "compliance dispute" to a panel according to Article 21.5 rests on both parties in the dispute. According to Norway, Article 21.5 does not specify

[170] Replies by Norway to questions from the European Communities, questions 3, 4 and 5, paras. 4 and 5.
[171] Replies by Norway to questions from the European Communities, questions 3, 4 and 5, para. 6.
[172] Replies by Norway to questions from the European Communities, questions 3, 4 and 5, para. 7.
[173] Replies by Norway to Panel questions, question 5 para. 10.
[174] Replies by Norway to questions from the European Communities, questions 3, 4 and 5, para. 8.
[175] Replies by Norway to Panel questions, question 5, paras. 11 and 12.

that it must be the original complainant to refer the matter to a "compliance panel". Norway submits that Article 21.5 is written in the passive form, concentrating on the result, specifically to place this obligation on all parties to the original dispute.[176]

5.107 Norway submits that the standard practice has been that the original complainant refers the matter to the panel. It argues that the one exception so far has been the referral to a compliance panel by the European Communities in *EC – Bananas III (Article 21.5 – EC)*.[177] According to Norway, the fact that the report remains unadopted and that the panel in that case refused to make any recommendations or rulings in the case, does not in itself prove that an original respondent may not invoke Article 21.5.[178] Rather, the position of the Panel in that case must be seen in the light of the fact that Ecuador also requested a separate compliance panel[179], and that the United States had submitted a request for retaliation that led to arbitration.[180] Norway submits that the panel in that particular case could thus justify not making any recommendations or rulings by pointing to these other proceedings.[181]

5.108 In Norway's view, a panel launched by the respondent cannot just make a declaratory judgment based on the presentation of the original respondent, but must make an objective assessment of the matter before it. The scope of the "terms of reference" would be to examine whether the measures taken to comply imply that there is now compliance with the rulings and recommendations of the original panel, *i.e.* that the original violation has been removed. Only the violations specifically addressed in the original report will be addressed by the compliance panel, not any other violations that the new measure may cause.[182]

5.109 Norway argues that where the original complainants refuse to participate, then any claim that the new measure is inconsistent with other provisions of the covered agreements will not be heard (will be outside of the "terms of the reference" for the compliance panel), and the original complainants risk a finding of compliance that does not take into account all the arguments that they would otherwise have presented. By not launching the Article 21.5 panel in a timely manner, the original complainants thus lose certain rights to present new claims that they would have had, had they themselves launched the panel request first. Such claims will thus have to await another panel. As such, the incentive structure that is created by allowing the original respondent to launch an Article 21.5 panel proceeding works to provide the original complainants with the incentive to go ahead themselves and launch the Article 21.5 panel first.[183]

5.110 In case a compliance panel is requested by the original respondent, the reference in Article 6.2 to "provide a brief summary of the legal basis of the complaint sufficient to present the problem

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[176] Joint reply by Norway to question 2 from the Panel and question 6 from the European Communities, para. 13.

[177] *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Article 21.5 by the European Communities*, Report by the Panel (WT/DS27/RW/EEC), 12 April 1999 – report never adopted.

[178] Joint reply by Norway to question 2 from the Panel and question 6 from the European Communities, para. 14.

[179] *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Article 21.5 by the Ecuador*, Report by the Panel (WT/DS27/RW/ECU), 12 April 1999.

[180] *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Arbitration by the European Communities under Article 22.6 of the DSU*, (WT/DS27/ARB), Report of the arbitrators dated 9 April 1999.

[181] See paras. 4.15 and 4.16 of the Panel Report in WT/DS27/RW/EEC.

[182] Joint reply by Norway to question 2 from the Panel and question 6 from the European Communities, paras. 16 and 18.

[183] Joint reply by Norway to question 2 from the Panel and question 6 from the European Communities, para. 16.

clearly" can be fulfilled by referring to the original panel report, together with the identification of the specific measure taken to comply and how it ensures compliance.[184] Where the original respondent has to request an Article 21.5 panel because the original complainants refused to do so, the original respondent may be considered as "complainant" for the purpose of Article 6.1 and "applicant" for the purpose of Article 6.2. The question who is "complainant" and who is "respondent" does not matter for the rest of the proceedings.[185]

H. SEPARATE CUSTOMS TERRITORY OF TAIWAN, PENGHU, KINMEN AND MATSU

1. Introduction

5.111 The Separate Customs Territory of Taiwan, Penghu, Kinmen and Matsu (Chinese Taipei) submits that it presents its views in this dispute because of the important systemic issues involved, in particular, the raised DSU provisions that are under negotiations in the Special Session of the Dispute Settlement Body. In its view, the resolution of certain issues in this case could significantly impact these negotiations.[186]

2. Opening Panel meetings for observation by the public

5.112 Chinese Taipei argues that in accordance with the procedures and customary practices developed over more than half a century under GATT, which are reflected in Articles 14.1, 18.2 and Appendix 3 of the DSU, panel proceedings are to be kept confidential. It argues that only Members by consensus can change the rules of confidentiality. According to Chinese Taipei, a panel, even with the consent of the parties does not have the legal authority to open the proceedings to the public.[187]

5.113 Chinese Taipei refers to Article VII of the Rules of Conduct which requires that each covered person shall at all times maintain the confidentiality of the dispute settlement deliberations and proceedings. According to it, the only exception to this confidentiality obligation is Article 18.2 of the DSU which states that nothing in the DSU shall preclude a party to a dispute from disclosing statements of its own positions to the public. Chinese Taipei is therefore of the opinion that this exception does not extend to the possibility of allowing parties to decide whether to open panel meetings to the public.[188]

5.114 According to Chinese Taipei, "panel deliberations" implies more than one form of deliberation, thus includes not only internal consideration among panelists, but also the entire process of the panel's consideration of the dispute.[189]

5.115 Chinese Taipei argues that the flexibility from Article 12.1 of the DSU to change Working Procedures in Appendix 3 cannot be extended to cover provisions in the Working Procedures that directly elaborate on the obligations of the DSU. It further argues that if the drafters had contemplated that the confidentiality requirement can be changed, they would have said so, just like in Article 18.2 of the DSU. In the absence of such language, only an amendment to the DSU by the Members through negotiations can change the requirement of confidential deliberations.[190]

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[184] Joint reply by Norway to question 2 from the Panel and question 6 from the European Communities, para. 18.
[185] Joint reply by Norway to question 2 from the Panel and question 6 from the European Communities, paras. 17 and 19.
[186] Third party submission of Chinese Taipei, para. 1.
[187] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, paras. 1 and 2.
[188] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, paras. 4 and 5.
[189] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, para. 3.
[190] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, paras. 6 and 7.

5.116 Chinese Taipei is of the opinion that the third party sessions be in closed session.[191]

3. Whether the DSB authorization remains in effect

5.117 Chinese Taipei contends that the new implementing measure is required to be confirmed by a multilateral determination that the measure is compliant with the DSB's recommendations and rulings. According to it, a unilateral claim of compliance together with the principle of good faith does not overturn the DSB authorization of suspension of concessions, and that suspension of concessions can continue until the conditions in Article 22.8 have been met.[192]

5.118 According to Chinese Taipei, the suspension of concessions can only be lifted after a multilateral determination of compliance, which involves an examination of the implementing measure against the recommendations and rulings of the DSB, or by mutual agreement of the parties. In its view, until then, the DSB authorization remains valid and the suspension of concessions may continue. Chinese Taipei further states that if none of the parties brings the implementing measure to the panel, whether through Article 21.5 or Article 22.8, the suspension of concessions may continue. It contends that without the initiation of a dispute that results in the examination of the implementing measure, the *status quo* would be considered as maintaining the existing balance of rights and obligations among WTO Members.[193]

5.119 Chinese Taipei does not consider that there is a need to justify the continuing suspension of concessions after the implementing Member's claim that it has complied with the DSB's recommendations and rulings.[194]

5.120 Chinese Taipei rejects the view that the lack of action for any period of time on the part of Canada constitutes an expression of Canada's determination. According to it, the existence of the determination by Canada cannot depend on such an indeterminate criteria as the length of time it takes for Canada to take action under Article 21.5 of the DSU. In its view, Article 22.8 of the DSU allows Canada to continue its suspension of concessions until one of the three conditions therein have been met.[195]

4. Article 21.5 of the DSU

5.121 Chinese Taipei considers that one of the ways to arrive at a multilateral determination in the current situation is through Article 21.5 of the DSU. With respect to the European Communities' argument that in absence of the initiation by Canada of an Article 21.5 compliance panel, the European Communities' implementing measure must be presumed to be compliant with WTO rules[196] and the continuation of the suspension of concessions by Canada would amount to a unilateral determination of a violation of WTO rules, it argues that Article 23.2(a) is valid only if two requirements are present in the text of Article 21.5,namely, (a) a deadline by which a 21.5 panel must be initiated, and (b) an obligation only on the original complaining party to initiate the proceeding.[197]

5.122 Chinese Taipei considers that neither one of these requirements currently exists in the text, nor is it reasonable to interpret their existence. It submits that it is up to the Member involved to choose whether and when to initiate the Article 21.5 proceeding. It opines that while it recognizes that the party suffering the suspension of concessions has an interest to lift such suspension as early as

[191] Replies by Chinese Taipei to Panel questions concerning open hearings, question 2, para. 12.
[192] Replies by Chinese Taipei to questions from the European Communities, question 1.
[193] Replies by Chinese Taipei to questions from the European Communities, question 4.
[194] Replies by Chinese Taipei to questions from the European Communities, question 5.
[195] Replies by Chinese Taipei to Panel questions, question 1.
[196] EC's first written submission, para. 61.
[197] Oral statement of Chinese Taipei, para. 2.

possible, that interest has to be balanced with the fact that the same party had originally been determined, through a lengthy WTO process, to be in violation of its obligations, and had a chance to implement, but failed to do so, within a reasonable period of time. Further, it argues that consistent with the text of Article 21.5, if the original respondent considers the conditions for the suspension of concessions to be no longer valid, the respondent may initiate the Article 21.5 proceeding at any time.[198]

5.123 Chinese Taipei stresses that as the DSU currently stands, there is no deadline and no designated party to initiate the Article 21.5 proceeding. Chinese Taipei agrees with the United States that just because the United States has not initiated the Article 21.5 proceeding does not mean that the European Communities automatically enjoys the presumption of compliance. In its view, at this stage, only a multilateral procedure can reach that conclusion, and one of the ways the European Communities can obtain such a multilateral determination is through its initiation of an Article 21.5 panel.

5.124 Chinese Taipei wishes to remind the Panel that the procedural issues involved in this case are currently under discussion in the negotiations on the improvement and clarification of the DSU. It argues that several competing proposals are on the table, including one from the European Communities. Chinese Taipei notes that it is a view widely shared by Members that the DSU procedures in this so-called "post-retaliation stage" are imperfect. According to Chinese Taipei however, it is not the task of the Panel, or indeed any Member, through litigation, to make up for such imperfection. Therefore, Chinese Taipei urges the Panel to avoid interpreting the current provisions in a way that would impose rules or requirements that are not written in the text.[199]

5. The relationship between Article 22.8 and Article 23 of the DSU

5.125 Chinese Taipei argues that Articles 23 and 22.8 apply to different situations and therefore should not be read together, as this would lead to a weakening of the WTO dispute settlement system. It contends that Article 22.8 differs from Article 23 in that it deals with the specific post-retaliation situation, outlining the conditions under which the suspension of the concessions pursuant to authorization from the DSB can be lifted. Chinese Taipei states that the general principle of resolving disputes under the multilateral system in Article 23 has been specifically modified by Article 22.8. Article 22.8 thus has its own independent set of requirements applicable specifically to the post-retaliation situation, apart from the general principles in Article 23.[200]

5.126 Chinese Taipei opines that the basis upon which European Communities builds its arguments for its interpretation of DSU Articles 23 and 22.8 is the general principle of good faith under which States are normally considered to act in conformity with their obligations.[201] Chinese Taipei agrees that Article 23.2(a) embodies that principle in prohibiting Members from making any unilateral determination to the effect that a violation has occurred.[202]

5.127 Chinese Taipei argues that by its title, Article 23 applies to the normal situations when the Member is responding to a perceived violation, nullification, impairment, or impediment, to which the Member is seeking remedy. It argues that this is the normal situation under which most cases begin and are first brought to the attention of the Dispute Settlement Body.[203]

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[198] Oral statement of Chinese Taipei, para. 3.
[199] Oral statement of Chinese Taipei, para. 4.
[200] Third party submission of Chinese Taipei, paras. 2 and 7.
[201] EC's first written submission para. 87.
[202] Third party submission of Chinese Taipei, paras. 2-4.
[203] Third party submission of Chinese Taipei, para. 5.

5.128 According to Chinese Taipei, Article 23.2 prescribes the actions Members may take in the normal situation described in Article 23.1. According to it, specifically, 23.2(a) prevents a Member from acting upon the unilateral perception of violation until it is validated under multilateral procedures. Chinese Taipei considers that this amounts to the presumption that a Member is normally considered to be acting in conformity with its obligations until a multilateral determination under the WTO says otherwise.[204]

5.129 Chinese Taipei posits that Article 22.8 on the other hand describes situations that depart from the norm. It submits that the general principle in Article 23 relating to normal situations therefore has limited application and must be modified by the specific requirements spelt out in Article 22.8. In its view, the situation at hand is one where the redress of violation has already been determined at least once through multilateral procedures and where suspension of concessions has been authorized. Chinese Taipei argues that the requirement is not that the suspension of concessions must be lifted in the absence of an adverse finding, but rather that the suspension shall be applied until the violation has been removed or any of the other two conditions in the provision have been met.[205]

5.130 According to Chinese Taipei, it therefore follows from this difference in situation and requirement that the normal presumption that a Member is considered to be in conformity with its obligations until proven otherwise in a multilateral determination does not apply. It contends that since Article 22.8 provides that the suspension of concessions can continue until the removal of the violation, the presumption here is that there is no removal of the violation until a multilateral determination says otherwise.[206]

5.131 Chinese Taipei contends that if the normal presumption were to apply to Article 22.8, despite the existence of a multilateral determination and authorization for retaliation, any offending Member can simply declare itself to have removed the violation. It submits that this would create the incentive for Members to implement partially or not at all, and drag the Member suspending concessions into an endless loop of Article 21.5 litigations.[207]

5.132 Chinese Taipei is of the view that under both normal and Article 22.8 situations, a multilateral determination is the prerequisite to any action that changes the existing balance of rights and obligations. It further notes that normally, a Member cannot seek redress of violation without a multilateral determination because a balance is presumed to exist. Similarly, Chinese Taipei argues that under the Article 22.8 situation where suspension of concessions is in place, that situation is the presumed balance, and that existing balance cannot be changed without another multilateral determination.[208]

5.133 Chinese Taipei thus argues that the suspension of concessions by Canada does not fall into the normal situation described in Article 23 and until a multilateral determination deems the European Communities' implementing measure to have removed the previously multilaterally determined inconsistency, the continuation of suspension of concessions by Canada does not violate the existing provisions of the DSU.[209]

[204] Third party submission of Chinese Taipei, para. 6.
[205] Third party submission of Chinese Taipei, para. 7.
[206] Third party submission of Chinese Taipei, para. 8.
[207] Third party submission of Chinese Taipei, para. 9.
[208] Third party submission of Chinese Taipei, para. 10.
[209] Third party submission of Chinese Taipei, para. 11.

I. UNITED STATES

1. Introduction

5.134 The United States submits that for all of the reasons set out in the arguments presented by the United States in *United States – Continued Suspension of Obligations in the EC – Hormones Dispute* (WT/DS320)[210] the United States concurs that Canada's continued suspension of concessions to the European Communities is consistent with the obligations of Canada under the DSU and GATT 1994.[211]

2. Opening Panel meetings for observation by the public

5.135 A summary of the arguments of the United States on the opening of panel meetings for observation by the public is set out in Section IV.B.2 of the Panel's Report in *United States – Continued Suspension of Obligations in the EC – Hormones Dispute* (WT/DS320).

VI. INTERIM REVIEW

A. INTRODUCTION

6.1 Pursuant to Article 15.3 of the DSU, the findings of the final panel report shall include a discussion of the arguments made by the parties at the interim review stage. This section of the Panel report provides such a discussion. As is clear from Article 15.3, this Section is part of the Panel's findings.

6.2 The European Communities and Canada separately requested an interim review by the Panel of certain aspects of the interim report issued to the Parties on 31 July 2007.[212] The European Communities stated that it stood ready to attend an interim review hearing to discuss the issues raised in its letter, "should the Panel consider it useful". The Panel notes that it is not for it to decide whether holding an interim review hearing would be useful. Article 15.2 of the DSU provides that it is "[a]t the request of a party [that] the panel shall hold a further meeting with the parties on the issues identified in the written comments." The Panel does not understand the EC statement above as a request by the European Communities for the Panel to hold an additional meeting with the parties. Furthermore, the Panel notes that Canada did not request such a meeting. As a result, the Panel did not hold an interim review meeting.

6.3 In accordance with the Panel working procedures and timetable, the parties had, and used, the opportunity to submit further written comments on each other's requests for review of specific aspects of the interim report.[213] These comments are discussed, where relevant, together with the request to which they relate.

6.4 The Panel issued its final report to the parties on a confidential basis on 21 December 2007.

6.5 The Panel has structured its treatment of the Parties' requests below in the following manner:

(a) first, it addresses a comment made in relation to the descriptive part of the report (Section IV) that the Panel could not address at an earlier stage of the proceedings;

[210] WT/DS320/6.
[211] Letter of 19 August 2005 to the Panel explaining the US third party submission.
[212] Letters of the parties dated 28 September 2007.
[213] Letters of the parties dated 19 October 2007.

(b) second, it discusses the comments of the parties relating to the findings of the Panel and, more particularly:

(i) the aspects of the report regarding procedural issues (Section VII.A);

(ii) the comments of the parties regarding the Panels findings of violation of Article 23.2(a) read together with Articles 21.5 and 23.1 of the DSU (Section VII.B); and

(iii) the comments of the parties regarding the compliance of the EC ban on meat and meat products treated with the six hormones at issue for growth promotion purposes with the *SPS Agreement* in relation to the Panel's findings on the EC claims on Article 23.1, read together with Articles 22.8 and 3.7 of the DSU (Section VII.C).

6.6 In addition, minor editing changes were made, which the Panel did not deem necessary to list in this section.

B. PARTIES' COMMENTS ON THE DESCRIPTIVE PART

6.7 The Panel considered and incorporated in its revised descriptive part the majority of the parties' comments. In one instance, however, the Panel rejected the modifications requested by the European Communities and deems it appropriate to provide its reasons in this section.

6.8 This instance relates to the EC request that the Panel incorporate in the descriptive part the parties' arguments on logistical issues relating to the opening to public observation of the Panel's substantive meetings with the parties and with the experts.

6.9 In its comments on paragraph 4.2 and following of the descriptive part of this report, the European Communities notes that, while the parties' answers of 20 June 2005 to a number of questions of the Panel have been reported in full, there is no reference to the parties' replies of 7 July 2005 to the additional questions of the Panel. This, in the opinion of the European Communities, raises a question of the completeness of the record of the parties' arguments. Inserting the replies of the parties of 7 July 2005 is also important according to the European Communities since the comments of the third parties on logistical matters have been reported in the descriptive part. Thus, the European Communities requests the Panel to reflect the parties' responses to these additional questions in its report.

6.10 The Panel notes that the parties' replies of 7 July 2005 essentially addressed technical questions of a logistical nature. The Panel did not deem it necessary to insert in its report any account of the logistical aspects of the opening of the hearings to public observation. The Panel notes in this respect that it did not include in the descriptive part of the report extracts from the replies of the parties of 20 June 2005 that related to logistical issues. Given that, among the third parties, only India and Mexico mentioned, in a general manner, the logistical implications of opening hearings to public observation, the discussion on logistical issues essentially took place between the parties themselves, or between the parties and the Secretariat. The Panel did not address the details of the logistical issues in its decision on opening meetings for public observation. This matter is, in the opinion of the Panel, purely administrative. It is neither procedurally nor factually relevant for the resolution of the dispute before us. The Panel is mindful that such an account might be useful from a practical point of view for future panels. However, it considers that the technical solutions found in this case may not necessarily be extended to other panel procedures, if only because the parties' expectations and constraints, e.g. in

terms of confidentiality, may be different in future cases.[214] Whereas the Panel provided a detailed account of the legal issues related to the opening of the Panel's hearings for public observation, for the reasons mentioned above, it decided not to follow the suggestion of the European Communities.

6.11 The Panel nonetheless wishes to confirm that the technical options available were extensively discussed with the parties and that the solution finally selected, i.e. the broadcast of the hearings into a separate room through closed-circuit television, was adopted in accordance with the positions expressed by the parties.

C. PARTIES' COMMENTS REGARDING THE FINDINGS OF THE PANEL

1. Preliminary remarks

6.12 As a preliminary remark, the Panel notes that the European Communities mentions in the introduction to its written request for the Panel to review precise aspects of the interim report that it:

> "[W]ill try to provide some examples of the numerous and serious errors in the reasoning of the Panel on the scientific issues underpinning this dispute. However, it is not possible in the time available to provide a detailed and complete list of all omissions and errors of the two interim reports as it would in reality require re-writing substantial parts of the Panel's report in order to rectify its analysis and reasoning... Therefore, the European Communities reserves the right to make all its comments at the appeal stage, if the Panel's findings on the issue were to be maintained."[215] (emphasis added)

6.13 This statement suggests that the European Communities did not identify all the precise aspects of the interim report with which it disagrees due to lack of time and because this would require rewriting substantial parts of the Panel report. It would, however, be able to make all its comments at the appeal stage. The Panel wishes first to make it clear that parties were free to request an extension if they needed more time to review the interim report and identify precise aspects that should be addressed by the Panel. The Panel notes in this respect that it is at the request of the European Communities that parties were granted several additional weeks to review the interim report. The Panel also notes that the European Communities gave as a justification for its request the expected length and complexity of the report. The Panel therefore regrets that the European Communities is now alleging lack of time as a justification for providing only "some examples" of errors in the reasoning of the Panel on the scientific issues underpinning this dispute.

6.14 In contrast, the European Communities mentions that it may make "all its comments" at the appeal stage. The Panel is surprised by the apparent choice of the European Communities to "make all its comments" before the Appellate Body rather than before the Panel, at the procedural stage expressly designed for the purpose of considering any and all comments on the interim report. This is because the decision of the European Communities to provide only "some examples" of errors of the Panel suggests that it has already decided to appeal the Panel report unless the Panel makes changes which the European Communities will not specify. It is also not clear whether the "examples" given by the European Communities exhaust all its factual comments or whether it intends to make further

[214] In the present dispute, after comparing different alternatives, the Secretariat was able to arrange open hearings through closed-circuit broadcast from one room to another utilizing the existing facilities of the Secretariat. The cost of open hearings was covered by the regular budget under the Secretariat arrangement. There may be different cost implications for future disputes in different circumstances but that consideration would fall outside the remit of this Panel.

[215] EC's written request of 28 September 2007, para. 5.

comments on factual issues before the Appellate Body. Having regard to Article 17.6 of the DSU, we consider this to be equivalent to depriving the interim review stage of its purpose.

6.15 The Panel therefore regrets that the European Communities did not request an extension so as to ensure that all the comments it deemed necessary on precise aspects of the interim report be made at the procedural stage of the dispute settlement process intended for that very purpose.

6.16 The Panel also notes that some of the EC comments are general statements on whole sections of the report, not a written request for the Panel to review *precise aspects* of the interim report. We recall that the panel in *Australia – Salmon*[216] stated as follows:

> "According to Canada, it is not open to the Panel to consider anything other than comments dealing with 'precise aspects' of the interim report. We agree with Canada and have therefore only reviewed our interim report in light of the comments made by the parties which relate to 'precise aspects' of the interim report."

6.17 We agree with the reasoning of the above-mentioned panel and therefore consider that the general comments by the European Communities did not require a specific reply from the Panel. We limited our replies to the portions of the report on which specific comments, in the form of precise requests for reconsideration of specific paragraphs, had been made by the European Communities. We addressed the EC general comments as part of our review of specific paragraphs.

2. Parties' requests for review related to aspects of the report on procedural issues

(a) Comments by the European Communities

6.18 The European Communities considers the Panel's reference to Article 17.10 of the DSU in paragraph 7.48 of the interim report is unnecessary and potentially detrimental as implicitly suggesting that the Appellate Body could be legally barred by Article 17.10 of the DSU from opening its own hearings to public observation. The European Communities requests that we remove that paragraph from our findings. We note that a similar request was made by Canada. Since this reference was only an additional argument, we accepted the parties' requests and removed our discussion of the term "proceedings" in Article 17.10 of the DSU.

6.19 The European Communities considers that the description of IARC contained in paragraph 7.76 footnote 370 is incomplete. It refers to Dr. Cogliano's statement in Annex G, paragraph 541. In paragraph 541, Dr. Cogliano essentially says that IARC monographs simply indicate which substances are carcinogenic or are probably not carcinogenic to humans. Monographs identify occurrence (i.e. exposure to a chemical through some particular pathway), but not the specific level of exposure for a particular population. Dr. Cogliano also says in paragraph 541 that different decision-making authorities will decide whether the evidence contained in IARC monographs sufficiently supports an SPS decision or whether they need to conduct further analysis. Thus it seems that IARC monographs provide information and serve in risk assessment. This said, the text in the footnote is a verbatim quote from the IARC website, describing what IARC does. Thus the Panel did not deem it necessary to augment the footnote.

6.20 The European Communities argues that the second sentence of paragraph 7.83 does not reflect reality, since the European Communities did not agree with the final decision on Working Procedures for Consultation with Scientific and/or Technical Experts adopted by the Panel. The Panel notes that, in a letter of 3 November 2005, the European Communities commented on the draft expert working procedures. One of the comments was that the experts should act as a single expert review

[216] Panel Report on *Australia – Salmon*, para. 7.3.

group in order to provide a consistent advice on the issues concerned. The European Communities also suggested that the experts should be independent from the industry or regulatory bodies which had a vested interest in the issue on which they would be consulted. The Panel rejected the EC request that experts should act as a single review group in its letter sent to the parties on 25 November 2005, together with its finalized Working Procedures for Consultation with Scientific and/or Technical Experts. We therefore modified paragraph 7.83 to reflect the absence of full agreement of the European Communities on the Panel's Working Procedures for Consultation with Scientific and/or Technical Experts.

6.21 The European Communities further requests us to redraft the fourth sentence of paragraph 7.83 to reflect better its concerns that two of the experts selected by the Panel participated in the preparation and drafting of the JECFA risk assessment of the hormonal substances at issue in this case, with which the EC risk assessment disagrees. The Panel sees no problem in clarifying the nature of the work of these two experts with JECFA It remains however puzzled by the EC suggestions that a scientist who worked with JECFA could be deemed to be biased in assessing the scientific evidence on which EC Directive 2003/74/EC relies and could be assumed to defend JECFA's work. First, scientists would readily admit that science is constantly evolving and the fact that new studies are peer reviewed is evidence that assessing new ideas and findings is part of scientific work. Assuming that scientists may lack objectivity because they participated in the preparation and drafting of JECFA's risk assessments on the hormones at issue would call into question the whole principle of peer review. The Panel also agrees with Canada in its comments on comments of 19 October 2007 that JECFA is the body that provides the independent scientific advice on which the work of Codex is based and Codex is expressly recognized by the *SPS Agreement* as having responsibilities for the establishment of "international standards, guidelines and recommendations". The Panel also recalls the role given to international standards, guidelines and recommendations by Article 3.1 and 3.2 of the *SPS Agreement*. It is therefore consistent with this role for the Panel to rely on experts who contributed in the preparation and drafting of JECFA's risk assessments of the substances at issue.

6.22 The Panel does not agree either with the EC arguments according to which the two experts at issue should not be described as "internationally recognized specialists". The Panel notes the arguments of Canada in this regard in its comments of 19 October 2007. The Panel recalls that these two experts have been selected by the FAO and WHO as part of the JECFA selection process. The selection procedure has been described in JECFA's reply to question 14 of the Panel to JECFA.[217] The Panel fails to understand why the JECFA selection would not be evidence of the international reputation of the scientists at issue.[218] The EC concerns about JECFA's work and the selection of experts to participate in that work are in contradiction with the role attributed by the *SPS Agreement* to Codex and to international standards, guidelines and recommendations. The Panel was fully aware of the area of expertise of the two scientists at issue, and believed that they would be more at liberty to comment on the content of JECFA's work than officials of the JECFA Secretariat. It also specified the reasons why those experts were selected in spite of their not having carried out experiments with the substances at issue and does not see any need for further substantial elaboration. The Panel has nevertheless made some clarifications, in response to the EC request, to paragraph 7.83.

6.23 The European Communities requests that we modify the first sentence of paragraph 7.85 to better reflect the content of its letter of 28 March 2006. We consider that the letter largely reiterated points which the Panel already addresses in paragraph 7.83, i.e. the involvement of experts in the preparation and drafting of JECFA's risk assessments and their alleged lack of scientific expertise. Besides this, the EC letter of 28 March deals exclusively with conflict of interest, which is the subject

[217] Annex E-2, pp. 115-116.

[218] See also Dr. Boobis, Annex G, para. 511; Dr. Tritscher, Annex G, para. 515; Dr. Wennberg, Annex G, para. 517.

addressed by the Panel in paragraph 7.85. While the Panel has modified the paragraph to reflect the fact that the EC letter addressed other issues already discussed in this report, it did not deem it necessary to modify the rest of the paragraph, except to clarify the elements on the basis of which the Panel considered that the experts concerned should be deemed to be the best among the very few individuals available.

6.24 Having reviewed the EC comments on paragraph 7.87 of the interim report**,** the Panel agrees that this paragraph did not directly relate to the issue of the alleged conflict of interest of two of the experts consulted by the Panel and has deleted it.

6.25 The European Communities argues that the statements in paragraph 7.115 and footnote 388 are not accurate as some of the subsequent evidence did expand and confirm the scientific basis of Directive 2003/74/EC. The European Communities refers to the replies of Dr. Guttenplan and Dr. Sippell. In paragraph 7.115 and footnote 388, the Panel states that nothing new was submitted after the adoption of Directive 2003/74/EC that differed *in any fundamental way* from previous evidence. This is not contradicted by the EC comment that subsequent evidence expanded and confirmed the scientific basis of its Directive, including the EC reply to question 5 of the Panel after the second substantive meeting.[219] The statements of Dr. Guttenplan referred to by the European Communities[220] do not support the EC argument. Dr. Sippell mentions in paragraph 611 of Annex G that he changed his opinion on exposure to exogenous oestrogens and precocious puberty because the acceptance of the significance of the ultrasensitive assays within paediatric endocrinology increased tremendously after he published his review article in 1999. However, the ultrasensitive assays he is referring to were not carried out or published after the adoption of Directive 2003/74/EC. In his written replies[221], where he discusses the ultrasensitive assay techniques, Dr. Sippell refers to *Klein et al (1994)* and *Larmore et al (2002)* and other studies dated 1999 or 2001. As a result, in the opinion of the Panel, the statement of Dr. Sippell cited by the European Communities is not about evidence that became available after the adoption of the Directive. Consequently the Panel did not modify paragraph 7.115 and footnote 388.

6.26 The European Communities also argues with respect to paragraph 7.116 that it had reserved its right to submit the finally published version of the study contained in Exhibit EC-107. According to the European Communities, this study was submitted in time and should have been accepted. The Panel notes that, when it submitted Exhibit EC-107 on 21 December 2005, the European Communities specified that it "reserve[d] its right to submit further evidence, if and to the extent this appears necessary for the purpose of commenting on any further submissions by the other parties as well as on replies of the panel's experts". The Panel does not read this reservation as reserving the EC right to submit the finally published version of the study. Moreover, the Panel recalls that the European Communities stated that it left it to the discretion of the Panel whether to forward the published version to the experts.[222] The Panel considers that it sufficiently explained in its report the reasons why the published version of this study had not been sent to the experts. In particular, it considered that submitting a modified study to experts at a relatively late stage of the expert consultation proceedings could generate confusion.

6.27 The European Communities also considers with respect to paragraph 7.124 that the Panel should accept that the European Communities submit the comments it wished to make in relation to some factual errors made by the United States[223] in its replies to the Panel questions posed after the

[219] Annex C, pp. 5-7.
[220] Annex G, paras. 709 and 713.
[221] Annex D, para. 319.
[222] See EC's letter to the Panel of 29 May 2006.
[223] Since the original request of the European Communities related to alleged factual errors in comments from the United States and Canada, and since the European Communities requests that we review

second substantive meeting. The Panel considers that its decision was clear. If inaccuracies resulting from US factual arguments had been reflected in the interim report, the European Communities could have identified them in its comments or in its comments on comments. There does not seem to be any need for the Panel to reverse its decision of 20 November 2006.

6.28 The European Communities also alleges, with respect to paragraph 7.126 *et seq.*, that one paragraph was added to the transcript of the experts' hearing annexed to this report compared with the version sent to the parties in January 2007. There are, indeed, more paragraph numbers. However, there is no additional text in Annex G as compared to the version sent to the parties in January 2007. In fact, the difference results from a correction to the paragraph numbers of the transcript. In the version sent to the parties for comments, there was a paragraph between paragraphs 29 and 30 that did not have a number. This paragraph became the new paragraph 30 in the final version of the transcript, and as a consequence, all the other paragraph numbers shifted by one. On the same subject, two more changes were made in paragraph numbers: paragraph 827 of the draft transcript was divided into two paragraphs, following a comment by the United States[224], and became paragraphs 828 and 829 in the final version of the transcript. Finally, another paragraph lacked a number, between paragraphs 926 and 927. This paragraph corresponded to a short statement by Dr. Boisseau clarifying that he had asked a question to Dr. Boobis, not to the European Communities. This unnumbered paragraph became paragraph 929. In conclusion, three additional paragraph numbers were added in the final version of the transcript compared to the draft version sent for comments to the parties. The draft version had 1069 numbered paragraphs; the final version has 1072 numbered paragraphs.

6.29 The European Communities also seems to request, with respect to paragraph 7.135**,** that the Panel specify the nature of the "editorial adjustments" made in the transcript. The Panel deems it appropriate to recall that the tapes of the meeting of the Panel with the experts were given to a typist who transcribed them. Two types of editorial adjustments were made to the transcript. First, the Secretariat proofread the transcript, identifying any words or passages the typist had misunderstood and checking these passages against the tapes. The type of errors identified were limited to confusions regarding technical terms (e.g. "N-point" instead of "endpoint"; "safe defactual" instead of "safety factor"[225] or "defactual threshold" instead of "de facto threshold"[226]). Other corrections involved minimal adjustments to sentences, for example to remove repeated words and occasionally adding punctuation marks. Once these corrections were made, the transcript was sent to the experts and subsequently to the parties in order to give each speaker the chance to verify that his or her own interventions had been accurately reflected. The experts' comments consisted of further corrections of technical words which had been improperly transcribed, or corrections of word order or colloquial expressions to make the transcript more legible. This is the reason why the Panel considered that these corrections did not go beyond "minimal editorial adjustments".

(b) Comments by Canada

6.30 With respect to the discussion of the procedural question of the opening of the Panel meetings with parties and experts for public observation, Canada requests that we remove our discussion of the term "proceedings" as it appears in Article 17.10 of the DSU. We note that the same request was made by the European Communities. Since this reference was only an additional argument, we accepted the parties' requests and removed our discussion of the term "proceedings" in Article 17.10 of the DSU.

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paragraph 7.124 of this report, the Panel deemed it appropriate to discuss this issue in this interim review section.

[224] See US's letter dated 14 February 2007.

[225] Annex G, para. 422.

[226] Annex G, para. 707.

6.31 Canada also requests that we modify paragraph 7.138. We see no reason not to adjust the description of the measure since it is actually the absence of recourse to the DSU by Canada which seems to be at the origin of the EC complaint. However, under the circumstances, we also deem it necessary to specify that the issue stems from the fact that Canada maintained the measure after the notification of Directive 2003/74/EC to the DSB and, accordingly, we have modified paragraphs 2.7 and 7.138.

6.32 Canada contests the conclusion of the Panel in paragraphs 7.149 and 7.151 that the European Communities narrowed the terms of reference of the Panel through the approach it followed in its first written submission. For Canada, the EC approach is a "choice of legal strategy" which is not binding on the Panel. The European Communities cannot constrain the terms of reference of the Panel by adopting a specific approach to its claims in its first written submission.

6.33 The Panel agrees that it is well established that a complainant cannot change the terms of reference of a panel in its first submission or subsequently. As stated by the Appellate Body in *EC – Bananas III*:

> "If a *claim* is not specified in the request for the establishment of a panel, then a faulty request cannot be subsequently 'cured' by a complaining party's argumentation in its first written submission to the panel or in any other submission or statement made later in the panel proceeding."[227]

6.34 However, the Panel does not believe that this is the issue in the present case. The European Communities did not try to cure a faulty request. It made its claims more specific. As the Panel itself noted[228], there could be several ways to find a violation of Article 23 of the DSU. The European Communities has clarified how it considered that this violation should be approached by the Panel. As stated by the Panel on *EC – Tube or Pipe Fittings*[229]:

> "In our view, it is in the nature of the Panel process that the claims made by a party may be progressively clarified and refined throughout the proceedings."

6.35 The Panel also quotes the Appellate Body in *US – Carbon Steel*.[230] It seems to be accepted that complainants can clarify their claims throughout the proceedings. In this instance however, it appears that Canada is concerned by the conclusion of the Panel that it is *bound* by these clarifications or that they are part of the Panel's terms of reference.

6.36 Panels are free to address claims in the order that they deem appropriate.[231] However, if a party specifies in its first written submission that a claim is raised in the alternative, can a panel disregard this clarification? To a lesser extent, can a panel disregard the fact that the complainant addressed the violation of a given provision in a particular way? Regarding the first question, it seems that panels should be bound by a claim made "in the alternative", as acknowledged by the Appellate Body.[232] Regarding the second question, the reply might be less clear and depend on the type of "clarification" made by the complainant. In the present case, the EC clarification had serious consequences on how the Panel could address the claims listed in the terms of reference. The European Communities did not claim a violation of Article 23 in general, but a violation of Article 23 as a consequence of a breach of Article 22.8 of the DSU. The Panel also notes the arguments of the

[227] Appellate Body Report on *EC – Bananas III*, paras. 141-143; Appellate Body Report on *US – Lead and Bismuth II*, paras. 72 and 73.
[228] See para.7.159.
[229] Panel Report on *EC – Tubes and Pipes Fittings*, para. 7.10.
[230] See para. 7.148.
[231] Appellate Body Report on *Canada – Wheat Exports and Grain Imports*, para. 126.
[232] See, e.g., Appellate Body Report on *EC – Selected Customs Matters*, para. 308.

European Communities in its comments of 19 October 2007. The Panel recalls, in particular, that the rights of the respondent or its ability to defend itself were in no way affected by the "narrowing" of its claims by the European Communities. The Panel remains of the view that it is bound by the EC approach to its claims and, accordingly, has not modified paragraph 7.149 or paragraph 7.151.

3. Comments of the parties regarding the Panel's findings of violation of Article 23.2(a) read together with Articles 21.5 and 23.1 of the DSU and on the EC claims on Article 23.1, read together with Articles 22.8 and 3.7 of the DSU

(a) Comments by the European Communities

6.37 The European Communities disagrees with the interpretation the Panel makes, in paragraph 7.153, as well as in paragraph 7.288**,** of the EC claims as set out in its first written submission. The European Communities insists in its comments that "it did not argue [in its main claims] that there was a violation of Article 22.8 itself, but rather one of Article 23.1". In other words, the European Communities seems to suggest that the Panel should not have addressed the conformity of Canada's measure under Article 22.8 of the DSU – even though this Article was listed in the EC request for establishment of a panel – but only under Article 23.1. Yet, the European Communities alleges a violation of Article 22.8 in various parts of its first submission and subsequently.[233]

6.38 In the opinion of the Panel, the use of the term "in conjunction with" or "read together with" is not indicative that the European Communities only claims a violation of Article 23. In Section III.E.3 of its first written submission, the European Communities alleges a violation of Article 3.7 even though in its conclusions it states that the United States' and Canada's unilateral conduct "violates Article 23.1 of the DSU read in conjunction with Article 22.8 and 3.7 of the DSU". One cannot conclude either that the European Communities draws a conclusion of violation of Article 22.8 from the violation of Article 23.1 since its allegation of violation of Article 23.1 stems from the obligation to withdraw the measure if the violation has been removed. Rather, one must conclude the opposite, i.e. that the European Communities draws a conclusion of violation of Article 23.1 from a violation of Article 22.8. For those reasons, the Panel does not agree with the argument made by the European Communities at the interim review stage that it never made a claim of violation of Article 22.8 of the DSU, and that its claims related only to violations of Article 23.

6.39 The European Communities also contests the qualifications made by the Panel of its second series of main claims (i.e. its claims of violation of Article 23.1 of the DSU in conjunction with Article 22.8 and Article 3.7 of the DSU) as claims "premised on compliance by the European Communities with the DSB recommendations and rulings in the *EC – Hormones* case" in paragraph 7.163. The Panel notes that it has clearly explained in paragraphs 7.293-7.294 why it believes that this claim was premised on compliance with the DSB recommendations and rulings in the *EC – Hormones* case.

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[233] See, for instance:
- EC's first written submission, para. 71: "Under Article 23.1 of the DSU, Canada is obliged to have recourse to, and abide by, the rules and procedures of this Understanding. This encompasses, *inter alia*, Articles 22.8 and 3.7 of the DSU";
- EC's first written submission, Section III.E.2, title: "The obligation not to apply suspension of concessions or other obligations under Article 22.8 of the DSU";
- EC's first written submission, Section III:E.3, title: "Canada's violation of Article 23.1 and Article 22.8 of the DSU necessary entails a violation of Article 3.7";
- EC's first written submission, para. 123: "For these reasons, Canada, by violating Articles 23.1, 22.8 of the DSU, also acted contrary to Article 3.7 of the DSU";
- EC's oral statement at first meeting, para. 56: a "systemic claim under Article 22.8, *in conjunction with Article 23.1*";
- EC's second written submission, para. 174.

6.40 Consequently, and having regard to Canada's comments of 19 October 2007, the Panel will not delete the section of its report considering the allegedly non-existent EC claim under Article 22.8 of the DSU.

6.41 The Panel, however, deems it appropriate to clarify paragraph 7.163, and to make a modification with respect to paragraph 7.357 in order to make clear that it is not reviewing the EC claim of violation of Article 22.8 in isolation.

6.42 The European Communities also argues that, even though the obligation of the respondent clearly emerges from the Panel's reasoning, the Panel should clarify its recommendations. This could be done either by removing from the findings any consideration of the second series of main EC claims (i.e. its claim of violation of Article 23.1 of the DSU in conjunction with Articles 22.8 and 3.7 of the DSU) or, if necessary, through suggestions under Article 19.1 of the DSU, or through clarifications in the Panel's reasoning. A somewhat similar request for clarification has been made by the respondent in its request for review of precise aspects of the interim report. However, the European Communities suggests that the Panel should clarify that Canada must remove its suspension of concessions, whereas Canada requests that we clarify that our findings under Article 23.1 and 23.2(a) have been rendered moot by the current proceedings and the Panel's findings regarding Canada's compliance with Article 22.8 of the DSU.

6.43 The Panel is mindful of its duty to assist the DSB in making recommendations or rulings aimed at achieving a satisfactory settlement of the matter. The Panel notes that the parties have both requested that the Panel make suggestions or concluding remarks aimed at clarifying what is expected from Canada. The Panel notes, however, that their proposed suggestions or concluding remarks are divergent. The Panel wishes to recall its conclusion in paragraph 7.244. This conclusion is based on the terms of Article 23.1 and 23.2(a). Those provisions require that recourse should be had to "the rules and procedures of the [DSU]" (Article 23.1) or, in the case of Article 23.2(a), that recourse be had to "dispute settlement in accordance with the rules and procedures of this Understanding". Moreover, for reasons explained in this report, the Panel does not believe that recourse by the European Communities to dispute settlement exempts the respondent from its obligations under Article 23.1 and 23.2(a) of the DSU. The Panel has clarified this point in paragraph 8.3.

(b) Comments by Canada

6.44 The Panel accepted Canada's suggestion regarding paragraph 7.225.

6.45 Canada requests that we clarify our statement in the first sentence of paragraph 7.292 by confirming that the present proceedings and the Panel's findings in respect of Article 22.8 of the DSU, while technically not findings under Article 21.5 of the DSU, involve the same legal questions and legal conclusions as a compliance panel under Article 21.5 of the DSU. While recognizing that, indeed, its review of a breach of Article 22.8 by Canada involved in this case assessments resembling those that could have been performed by an Article 21.5 panel called upon to review the compatibility of Directive 2003/74/EC, the Panel notes a fundamental difference. The matter before it is not the conformity of Directive 2003/74/EC, but the conformity of the continued suspension of concessions or other obligations by Canada *vis-à-vis* the European Communities. The fact that the European Communities may have the possibility in practice to achieve, by initiating a panel procedure like the present one, a result similar to that which could be achieved by Canada having recourse to Article 21.5 does not exempt Canada from its obligation under Article 23 to have recourse to dispute settlement. Moreover, there is no telling which claims would be brought by Canada if it had recourse

to Article 21.5 of the DSU. We also note the EC comments of 19 October 2007.[234] As a result, the Panel does not deem it necessary to modify paragraph 7.292.

6.46 Canada requests that the Panel modify paragraph 7.358 so as to state that reviewing alleged violations of the *SPS Agreement* falls within the Panel's mandate and constitutes an integral part of its findings in this report.

6.47 The European Communities, in its comments of 19 October 2007[235], disagrees with the comments of Canada to the extent that, unlike in the case referred to by Canada where there was an express reference to another provision in the article allegedly breached, there is no reference in the term "removed" in Article 22.8 to any other provision. The European Communities considers that if Canada's interpretation prevailed, the responding party would effectively be free to refer to any provision of the covered agreements and the terms of reference would become meaningless.

6.48 The Panel considers that it has extensively explained why it believes that, while making actual findings regarding the compatibility of the EC Directive 2003/74/EC with the *SPS Agreement* is not part of its mandate, it has jurisdiction to address the compatibility of the Directive with the *SPS Agreement* to the extent necessary to make findings in relation to Article 22.8 of the DSU, which is part of its mandate. The Panel notes that this is part of its duty to make an objective assessment of the matter pursuant to Article 11 of the DSU and a sentence has been added to that effect in the findings.[236] The Panel also believes that its approach is consistent with the scope of a panel mandate as confirmed by the Appellate Body.

6.49 Moreover, the Panel considers that the Appellate Body report in *Argentina – Footwear (EC)*[237] does not support the view that the Panel could make actual findings with respect to the compatibility of the EC measure with the *SPS Agreement*. First, the EC implementing measure (Directive 2003/74/EC) is not part of the terms of reference of the Panel. Second, the Appellate Body report in *Argentina – Footwear (EC)* confirms the reasoning of the Panel:

> "We have examined the specific paragraphs in the Panel Report cited by Argentina, and we see no *finding* by the Panel that Argentina acted inconsistently with Article 3 of the *Agreement on Safeguards*. In one instance[238], the Panel referred to Article 3 parenthetically in support of its reasoning on Article 4.2(a) of the *Agreement on Safeguards*. Every other reference to Article 3 cited by Argentina was made by the Panel in conjunction with the Panel's reasoning and findings relating to Article 4.2(c) of the *Agreement on Safeguards*. None of these references constitutes a legal finding or conclusion by the Panel regarding Article 3 itself."[239]

6.50 In that case, the panel had reviewed Article 3 of the *Agreement on Safeguards* as part of its review of Article 4.2(a), not as a finding on Article 3. Article 3 was not mentioned in the terms of reference of the panel. The Appellate Body agreed with the panel that it had to consider Article 3. It even concluded that it had an obligation to do so. But it also noted that the panel made no findings under Article 3. Rather, its consideration of Article 3 was made in support of its reasoning on Article 4.2(a).

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[234] Paras. 14-16.
[235] Para. 21.
[236] Para. 7.374.
[237] Appellate Body Report on *Argentina – Footwear (EC)*, paras. 74-75.
[238] (*footnote original*) Panel Report, para. 8.238.
[239] Appellate Body Report on *Argentina – Footwear (EC)*, para. 73.

6.51 Finally, Canada requests a modification to paragraph 8.2 and the addition of a new paragraph confirming that the Panel's finding of a breach of Article 23.1 and 23.2(a) has been rendered moot by the current proceedings and the Panel's findings regarding Canada's compliance with Article 22.8 of the DSU. Regarding paragraph 8.2, having duly considered the EC comments on comments, we nonetheless decided to replace the term "legislation" with the term "measure", consistent with Article 19.1 of the DSU. Indeed, the measure at issue has been previously defined in paragraph 7.138.

6.52 Regarding Canada's request for the addition of a new paragraph, we do not agree with Canada that, through our comment in the first sentence of paragraph 7.350, we have recognized that recourse to Article 21.5 of the DSU has become unnecessary by virtue of the current proceedings. What we meant was that this dispute was an alternative to a recourse to Article 21.5 *by the European Communities*, not that it was an alternative to Canada complying with its obligations under Article 23.1 and 23.2(a) of the DSU. We have clarified this point in paragraph 8.3.

4. Comments of the parties on the compliance of the EC ban on meat and meat products treated with the six hormones at issue for growth promotion purposes with the *SPS Agreement* in relation to the Panel's findings on the EC claims on Article 23.1, read together with Articles 22.8 and 3.7 of the DSU

(a) Comments by the European Communities

(i) Introductory comments

6.53 In an introduction to its specific comments, the European Communities alleges:

(a) that the Panel has dismissed the 1999, 2000 and 2002 Opinions as not constituting a proper risk assessment based on an alleged absence of specific evidence which, the European Communities claims, is impossible to provide;

(b) that the Panel dismissed the Opinions as not having presented sufficient evidence to call into question the conclusions of JECFA;

(c) that the Panel should have scrutinized JECFA's evaluations, which are based on old studies which were not publicly available and were not communicated to the Panel or the Panel's experts for review;

(d) that the Panel has reached its conclusions on the EC implementing measure (Directive 2003/74/EC) by relying selectively, for a number of important issues, on the statements of two experts in a group of six. The European Communities recalls that those two experts had participated in the drafting of the JECFA's assessments contradicted by the EC Opinions and were obviously defending their own work and the methodology applied by JECFA and Codex. Comparatively, the other four experts had overall validated and supported the conclusions of the EC Opinions; and, finally,

(e) that the Panel's methodology and reasoning are contrary to established principles on burden of proof and standards of review of genuine scientific questions by WTO panels and ordinary courts of law.

6.54 Regarding the argument under (a) above, the Panel will address this question when it addresses the EC comments on the Panel's findings under Article 5.1 of the *SPS Agreement*. As a preliminary remark, however, the Panel wishes to clarify that it did not "dismiss the opinion of a relevant committee constituted of highly regarded, independent scientific experts". The Panel

concluded that the European Communities had not evaluated specifically the possibility that the adverse effects related to the association between excess hormones and neurobiological, developmental, reproductive and immunological effects, as well as immunotoxicity, genotoxicity and carcinogenicity coming into being, originating or resulting from the consumption of meat or meat products which contain veterinary residues of oestradiol-17β as a result of the cattle being treated with this hormone for growth promotion purposes. The Panel also found that the scientific evidence referred to in the Opinions does not support the EC conclusions on genotoxicity, or the conclusion that the presence of residues of oestradiol-17β in meat and meat products as a result of a cattle being treated with this hormone for growth promotion purposes leads to increase cancer risk. Nor does the scientific evidence support the EC conclusions about the adverse immunological and developmental effects of consuming meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes. This does not put into question the results of the studies and research relied upon by the SCVPH, nor the conclusions reached by the scientists, but simply the conclusions drawn by the European Communities on the basis of the science.

6.55 Regarding the argument under (b) above, it is correct that the Panel considered that, in order to determine whether relevant scientific evidence was insufficient within the meaning of Article 5.7 of the *SPS Agreement*, it had to take the results of the risk assessments made by JECFA as a "benchmark" of the existence of sufficient scientific evidence. This is in line with the findings of the Appellate Body in *Japan – Apples* that the relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*[240], as well as with the presumption of compliance under Article 3.2 of the *SPS Agreement*.

6.56 As far as the argument under (c) is concerned, the Panel explained in its findings why it relied on JECFA's work without questioning it.[241] First, using JECFA's risk assessments as "benchmarks" did not mean that the Panel had to examine the scientific evidence supporting JECFA's conclusions. Second, none of the parties contested that JECFA and Codex work on the hormones at issue (with the exception of MGA) constitute international standards, guidelines and recommendations within the meaning of Article 3.2. Because sanitary measures which conform to international standards, guidelines or recommendations are deemed to be consistent with the provisions of the *SPS Agreement*, the Panel had no reason to scrutinize the evaluation made by JECFA. The only benefit of such an evaluation would have been to determine whether JECFA's risk assessment met the conditions of Article 5.1. However, the question before the Panel is not to review the validity of international standards – the Panel has no mandate to do that. It is not to review whether JECFA's risk assessments are compatible with Article 5.1, but whether the EC implementing measure is compatible with Article 5.1 as far as oestradiol-17β is concerned or justified under Article 5.7 for the other five hormones at issue. The Panel also notes in this respect that, whereas Members have, pursuant to Article 3.3, a right to introduce or maintain sanitary measures which result in a higher level of sanitary protection than would be achieved by measures based on the relevant international standards, guidelines and recommendations, the way to do this is not by seeking to demonstrate that those standards, guidelines and recommendations are flawed or outdated, which would simply show that they have become insufficient and would not justify the EC measure, but by providing positive evidence or information supporting the conformity of the measure at issue with Article 5.1 and/or Article 5.7. It was, thus, for the European Communities to provide convincing evidence, in line with the requirements of Article 3.3 of the *SPS Agreement*, to justify its definitive ban on oestradiol-17β and that relevant scientific evidence was insufficient for the other five hormones.

[240] Appellate Body Report on *Japan – Apples*, para. 179.
[241] Paras. 7.621-7.625.

6.57 Regarding the argument according to which the two experts involved in the drafting of JECFA's risk assessments were defending their own work and the methodology applied by JECFA and Codex, the Panel wishes to add to what it has already said above that, since JECFA's risk assessments were used as the reference risk assessments for purposes of the analysis under Article 5.7 of the *SPS Agreement*, it was necessary for the Panel to be able to rely on the advice of experts intimately knowledgeable about the substance of JECFA's risk assessments.[242] The purpose was not to check whether JECFA's risk assessments were supported by sufficient scientific evidence or carried out in accordance with Article 5 of the *SPS Agreement*, but to identify to what extent the concerns raised by the European Communities in its submissions had been considered in the development of its risk assessments by JECFA (e.g. how the risk to prepubertal children had been taken into account by JECFA). Second, the Panel recalls that JECFA is an international, independent entity composed of highly qualified experts selected by the WHO or FAO according to strict procedures.[243] JECFA also regularly reassesses its risk assessments, normally at the request of Members of Codex, and evidence before the Panel suggest that the European Communities did not request JECFA to reassess the hormones at issue on the basis of the new evidence it had gathered. Instead, the European Communities relied on its own risk assessment. Moreover, JECFA reaches its conclusions by consensus. So the opinions expressed by the two experts were given with regard to the consensual view of JECFA on this matter, not just their own personal positions in the past. This does not mean, however, that JECFA's work is these particular experts' own work: it is a joint work by several experts. The experts that the European Communities claims were defending their work acknowledge that the state of knowledge can evolve. For instance, Dr. Boobis stated that:

> "[S]cience moves on, and it would be complacent for a risk assessment body to assume that it knew everything about a substance at a particular point in time. We have to work within the available information, and the question we ask is: do we have sufficient information at this point to conduct a risk assessment? – not: is the data complete and are there no scientific questions remaining to be answered."[244]

6.58 The experts consulted by the Panel are used to considering and peer reviewing studies that go beyond what they have published themselves or perhaps even contradict them. In other words, they are not likely to feel any need to defend their own previous work results in the light of new, convincing evidence or techniques that put such previous work into doubt. The Panel also notes that other experts referred to JECFA's work in their replies, just as they also referred to studies commissioned by the European Communities.[245]

6.59 The European Communities also argues that the remaining four experts "overall validated and supported the conclusions of the [SCVPH] Opinion[s]". The Panel does not share this point of view. First, not all experts expressed their views on all the issues. The experts who expressed their views often agreed with each other. Second, the impression that a majority of experts overall validated and supported the conclusions of the SCVPH Opinions is incorrect. With respect to the five provisionally banned hormones, to different degrees, the experts agreed that new studies would be useful. This does not mean, however, that they considered them useful for the reasons advocated by the European Communities. The four experts agreed regarding the hazard related to hormones, or the risk attached to high doses. But so did the two experts with JECFA experience.

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[242] In order to assess the appropriateness for the Panel to seek advice from experts involved in the preparation of JECFA's risk assessment, it is also important to recall that the experts are being consulted in the context of an assessment of the EC implementing measure under Articles 5.1 (and accessorily 5.2 in WT/DS320), 5.7 and 3.3 of the *SPS Agreement*, and of the presumption of conformity with the *SPS Agreement* of measures based on international standards.

[243] JECFA's reply to question 14 of the Panel. See also Dr. Boobis, Annex G, para. 511; Dr. Tritscher, Annex G, para. 515; Dr. Wennberg, Annex G, para. 517.

[244] See Annex G, para. 346.

[245] See, e.g. Dr. Guttenplan, Annex D, para. 145.

6.60 As to the argument that the Panel's methodology and reasoning are contrary to established principles on burden of proof and standards of review of genuine scientific questions by WTO panels and ordinary courts of law, the Panel wishes to recall its findings at paragraphs 7.377-7.383 and 7.403-7.418 on the standard of review and burden of proof. The Panel has also explained why it gave particular relevance to JECFA's risk assessments and why, to the extent that the European Communities disagreed with JECFA, it had to prove that its measure was based on a risk assessment consistent with Article 5.1 and Annex A(4) of the *SPS Agreement*, or that the relevant scientific evidence was insufficient.

6.61 The European Communities argues that the statement originally found in paragraph 7.368 was not accurate as the European Communities was allegedly replying to a hypothetical question and stated that it was not necessary to look into the scientific issues. The Panel notes that the European Communities stated in its reply to question 74 of the Panel[246] that "it did not believe that it [was] necessary to look into the scientific issues". The European Communities did not formally *object* to the Panel seeking scientific opinion even if the Panel proceeded with reviewing the *SPS Agreement*. Indeed, the European Communities added in its reply to the same question 74:[247]

> "However, the European Communities does not believe that the Panel would have the expertise to decide on such issues itself, should the Panel decide to go down [the road] of deciding the scientific issues at stake. In such a scenario, the European Communities believes that the consultation of scientific and technical advice would be absolutely necessary."

6.62 The European Communities argues that it was replying to an hypothetical question. Yet, the European Communities uses the affirmative and not the conditional in its reply when it states that "New experts will have to be chosen".[248] The Panel concludes that, whereas the European Communities was not of the view that it was necessary to look into the scientific issues, it was nevertheless in favour of the consultation of scientific experts if the Panel decided to address the scientific issues at stake. Paragraph 7.368 was modified accordingly.

6.63 The European Communities suggests that the Panel contradicted itself in paragraph 7.371 when it stated, on the one hand, that parties had had sufficient opportunity to comment on the other party's allegations and, on the other hand, in paragraph 7.124, refused to allow the European Communities clarify the nature of a number of factual errors allegedly made by the United States and Canada. In paragraph 7.124, the Panel took the view that the European Communities should not be allowed to make further comments, lest the other parties would also comment and this would launch an endless exchange of arguments. The Panel notes that parties were allowed to comment on the experts' responses and to comment on the comments of the other party. In addition, the parties were allowed to comment on each other's replies to the questions of the Panel after the second substantive meeting. This is fully consistent with usual panel procedures. Moreover, the European Communities could correct any factual error appearing in the interim report by requesting the Panel to review precise aspects of the interim report, if the allegedly erroneous information provided by the United States and Canada had been used in the findings. The Panel notes that the EC request to correct some factual statements made by the other parties was limited to factual aspects, not to legal issues such as allegations of inconsistency with the *SPS Agreement*, which was the subject of this paragraph. The Panel nonetheless decided to clarify paragraph 7.371**.**

[246] EC's replies to Panel questions after the first substantive meeting, Annex B, para. 274.

[247] EC's replies to Panel questions after the first substantive meeting, Annex B, para. 275.

[248] The Panel also notes that the European Communities made an alternative claim of violation of Article 22.8 of the DSU and Articles I and II of the GATT 1994, in isolation from its claim under Articles 23.1 and 3.7 of the DSU which was based on an allegation of actual compliance with the recommendations and rulings of the DSB in the *EC – Hormones* case.

6.64 The European Communities argues that, in paragraphs 7.373-7.374, the Panel states that its approach was a "pragmatic solution" and the "most logical way forward" without further explanation. The European Communities considers that the approach of the Panel is arbitrary and negatively affects the interests of the parties and reverses existing case law and established practice. The Panel first notes that the European Communities does not specify which "existing case law" and "established practice" it refers to, and that it does not make any reference to its previous submissions. Second, the Panel notes that these paragraphs contain only additional arguments. The Panel has amply justified its decision to address the compatibility of the EC implementing measure with the *SPS Agreement* throughout the preceding paragraphs. The Panel also explains the reason why it follows this approach in paragraph 7.374, emphasizing the need to assist the parties and the DSB in solving this dispute and the need to determine whether there is a violation of Article 23.1 in conjunction with Article 22.8 and Article 3.7 of the DSU. The Panel's choice was directed by the requirement to make an objective assessment of the matter before it, in accordance with Article 11 of the DSU, having regard to the particular circumstances of this case, as recalled in Section VII.C.2.(a) of this report.

6.65 The European Communities states that paragraph 7.401 and footnote 506 are factually inaccurate. This comment can only relate to and be limited to the refusal of the Panel to let the European Communities correct alleged *factual* errors in the comments of Canada and the United States on the EC replies to the questions of the Panel after the second substantive meeting. First, the European Communities never identified the factual errors at issue. Second, the Panel explained its position in its letter of 20 November 2006. The Panel recalls that it followed the standard practice of panels in terms of procedure, allowing comments on replies to the questions of the Panel. The Panel felt justified in not allowing further comments. The Panel stressed that the European Communities could address these factual errors at the interim review stage, if they were reflected in the findings of the Panel. It appears that the European Communities did not take advantage of this opportunity as no such factual corrections were made. Thus, the Panel sees no reason to correct paragraph 7.401 and footnote 506.

6.66 The reference to Article 5.2 of the *SPS Agreement* in paragraph 7.434 has been removed.

6.67 The European Communities argues, with respect to paragraph 7.411, that the Panel misconstrued its role by engaging in settling a scientific debate and arbitrating the opinions expressed by the scientific community by "picking and choosing" from individual replies of experts without any valid explanation. The Panel explained in its findings in paragraph 7.69 why it deemed it preferable to consult experts individually. The Panel had also explained in its letter to the parties of 25 November 2005 how it understood its role in terms of assessment of scientific opinions. The Panel believes that weighing the scientific evidence before it was necessary to reply to the two main legal questions in relation to the *SPS Agreement*, i.e. whether the European Communities had performed a risk assessment within the meaning of Article 5.1 for oestradiol-17β and if the relevant scientific evidence was sufficient within the meaning of Article 5.7 as far as the other hormones were concerned. In fact, the Appellate Body confirmed the discretion of Panels in weighing evidence in *EC – Asbestos*.[249] This is also part of the role of panels under Articles 11 and 13 of the DSU. The Panel also considers that the role of the experts was to act as an "interface" between the scientific evidence and the Panel, so as to allow it to perform its task as the trier of fact. If panels were not to weigh the scientific evidence before them, then the DSU would have mandated the recourse to experts review groups. The Panel also notes that the Appellate Body took the view in *EC – Hormones*, that both the *SPS Agreement* and the DSU leave to the discretion of a panel the determination of whether the establishment of an expert review group is necessary or appropriate.[250] The Panel explained its approach in detail in paragraph 7.411 and thus does not believe that it engaged into "picking and

[249] Appellate Body Report on *EC – Asbestos*, para. 161.
[250] See para. 7.72.

choosing" without any valid explanation. The Panel notes that some replies to its questions were more detailed than others and supported by bibliographical references. The Panel believes that, in case of divergence of opinions between the experts, and having due regard to the comments of the parties and the clarifications provided by the experts at the meeting with the Panel, it was a sound approach to take into account, in forming its own opinion, the opinions that were the most precise and elaborate. Therefore, having also considered the comments of the respondent of 19 October 2007, the Panel did not deem it necessary to revise paragraph 7.411.

6.68 The European Communities considers that, in paragraphs 7.414-7.418, the Panel missed the point made by the European Communities, namely that neither the United States, Canada nor JECFA have provided conclusive proof that the methods used to generate the outdated evidence on which they based and continue to base their risk assessment were validated. The Panel first notes that the paragraphs at issue are part of an introductory section, not one where the validity of the evidence actually relied upon by JECFA is being discussed. Second, the purpose of the discussion contained in the paragraphs at issue is clearly stated in paragraph 7.418. The point made by the Panel is that a study is not *ipso facto* irrelevant because it is old. The Panel makes two points in paragraph 7.418: (i) that accuracy is a problem when one is at the limits of detection of the older methods and (ii) that in any event an essential question is whether a given method has been validated.

6.69 Second, the European Communities' comment raises the question whether there is a need for the United States and Canada to prove that JECFA's risk assessments were based on validated studies. In the opinion of the Panel, this is not a question that needs to be addressed in order to resolve this dispute. JECFA's risk assessments were used as the bases for Codex recommendations which are, pursuant to Article 3.1 and Annex A(3) of the *SPS Agreement*, "international standards, guidelines or recommendations". Pursuant to Article 3.3, it is for the WTO Member wishing to introduce or maintain sanitary measures which result in a higher level of sanitary protection than would be achieved by measures based on the relevant international standards, guidelines and recommendations to provide scientific justification in support of such measures. In that context, the question before the Panel is not whether JECFA's risk assessments were based on validated studies[251], but whether the European Communities' permanent ban on meat and meat products containing veterinary residues of oestradiol-17β derived from cattle treated with this hormone for growth promotion purposes is based on a risk assessment within the meaning of Article 5.1 and, for the five provisionally banned

[251] The Panel did not use the quotation from Dr. Wennberg in paragraph 7.417 to argue that JECFA's studies were actually validated, but to stress that if a study used a validated method, there is no reason to reject it simply because it is old. The problem with some of the more recent studies on which the European Communities relies is that they have not been validated. The European Communities also refers to statements of Dr. De Brabander (Annex G, paras. 670, 675, 681 and 687) and Dr. Sippell (Annex G, para. 689). The Panel understands from Dr. De Brabander's comments that there would be reasons to re-do certain assessments, *inter alia* because the separation power of components has increased considerably since the 1980s (see para. 681). However, the Panel notes that Dr. De Brabander insists on the fact that one cannot say that the "old" data are not correct on not valid until they are checked with modern analytical methods, which, according to him, has not been done. Dr. Sippell states that, for infant and young children, a standard commercially available radioimmunoassay is not able to pick up the real concentrations, because there are numerous other cross-reacting steroids. Dr. Sippell concludes that "one should really look at the new data". Whereas this statement suggests that old data are not valid, Dr. Sippel stops short of formally concluding that they are not valid. We also note Dr. Boobis' comment following Dr. Sippell's intervention (Annex G, para. 691):

> "I would make the point that a method that is used to measure low levels of oestrogens in infants is a different question from a method that is being used to measure residues in food. The analytical challenges are quite different and the methods that were developed in the 1980s for the residues were fit for that purpose, and that is what they were used for. If you ask the question about the circulating concentrations, that is a different issue. So in terms of residues the methods were suitable."

hormones, whether there exists *validated* studies that sufficiently put into question the evidence on which JECFA's risk assessments are based, so as to support a conclusion that the relevant scientific evidence is insufficient to permit the assessment of risk.

(ii) General comments on the Panel's analysis regarding oestradiol-17β

6.70 The European Communities argues that the use of the term "measure" in paragraphs 7.432 and 7.490 to describe the Panel's function is unfortunate because "it is clear that a panel does not measure anything (which implies that there is something quantitative to measure), but simply examines the conformity of the measure with the relevant provisions."[252] The Panel notes that it used the term "measure" in the sense, as defined by the Oxford English Dictionary, to "judge or estimate the greatness or value of (a person, a quality, etc.) by a certain standard or rule; appraise by comparison with something else."[253] The Panel believes that judging or appraising something, in this case the SCVPH Opinions, against a certain standard or rule, in this case Article 5.1 and Annex A(4) of the *SPS Agreement*, is precisely examining the conformity of the measure with the relevant provisions. Therefore, the Panel will not change the term. However, the Panel wishes to clarify here that it did not intend to use the term "measure" to imply any sort of quantitative analysis.

6.71 The European Communities also states that it did not understand the Panel's use of the term "objective measures" in the paragraph of the interim report corresponding to paragraph 7.432. The European Communities correctly points out an error in the paragraph. The fourth sentence should read "The Panel must objectively measure the Opinions against the relevant standard for whether a risk assessment has been conducted, which can be found in the texts of Articles 5.1 as well as Annex A(4) of the *SPS Agreement*." Again, the Panel notes that it is using the term "measure" in the sense of a qualitative appraisal of the SCVPH Opinions against a standard or rule, namely the *SPS Agreement*.

(iii) Comments on "risk assessment techniques"

6.72 The European Communities argues that the discussion by the Panel of risk assessment techniques in paragraphs 7.435-7.459 is irrelevant and unnecessary given that no relevant international risk assessment techniques for veterinary drug residues have been agreed upon.[254]

6.73 The Panel notes that Article 5.1 requires that Members take into account the risk assessment techniques of the relevant international organizations when ensuring that their sanitary and phytosanitary measures are based on a risk assessment. Therefore, the Panel believes that an analysis of whether such techniques exist and whether the European Communities took them into account is necessary and appropriate to an analysis of whether the European Communities has removed the previously found inconsistency of its ban on the importation of meat and meat products treated with oestradiol-17β for growth promotion purposes with Article 5.1 of the *SPS Agreement*.

6.74 The Panel notes in paragraph 7.438 that no specific techniques or guidelines has thus far been formally adopted by Codex for use by national governments in conducting risk assessments of veterinary drug residues. However, there are relevant definitions of the phases of a risk assessment as well as guidelines and practices for conducting a risk assessment in the general sense and the Panel, therefore, analyses whether the European Communities took these into account when it adopted Directive 2003/74/EC.

[252] EC's comments on interim report, para. 50.
[253] *Shorter Oxford English Dictionary*, 5th edition (1993), p. 1730.
[254] EC's comments on interim report, para. 51.

6.75 The European Communities also argues that these passages convey the erroneous message that the concept of risk assessment as defined in the *SPS Agreement* is the same as in Codex Alimentarius.[255]

6.76 The Panel is surprised by this comment, because it states in paragraph 7.457:

> "[T]he Panel must concur with the reasoning of the panel in *Japan – Apples*, that the requirement to "take into account" the risk assessment techniques of international organizations:
>
> > '[D]oes not impose that a risk assessment under Article 5.1 be 'based on' or 'in conformity with' such risk assessment techniques. This suggests that such techniques should be considered relevant, but that a failure to respect each and every aspect of them would not necessarily, *per se*, signal that the risk assessment on which the measure is based is not in conformity with the requirements of Article 5.1.'"[256]

6.77 The Panel finds that this quotation adequately conveys the Panel's opinion that although the risk assessment techniques of the relevant international organizations must be considered by the Members, they are not binding on Members and that not following them would not necessarily lead to the conclusion that the risk assessment did not conform with Article 5.1 and Annex A(4) of the *SPS Agreement*. However, to avoid confusion, the Panel clarified paragraph 7.457 and added paragraph 7.458.

6.78 The European Communities also takes issue with paragraph 7.444. In that paragraph the Panel summarizes the arguments of the European Communities as follows:

> "The **European Communities** agrees that the risk assessment techniques developed by Codex are relevant and contemplated in Article 5.1's requirement to take into account the risk assessment techniques developed by relevant international organizations."

6.79 The European Communities argues that this paragraph is misleading because the European Communities has followed the four steps of risk assessment described by Codex. The European Communities asserts that it has followed the four steps because its legislation so provides, not because it is required to do so under the *SPS Agreement*, since such techniques do not exist.

6.80 The Panel notes that it does not discuss in any way in paragraph 7.444 whether the European Communities has complied with the four steps. In addition, the Panel notes in paragraph 7.446 that "the European Communities argues that the risk assessment at the basis of Directive 2003/74/EC precisely follows the four steps of risk assessment as defined by Codex ..."

6.81 It is irrelevant for the Panel whether the EC internal legislation mandates that the European Communities follow the four steps or whether the European Communities complied with its own legislation. The Panel's analysis focuses on whether the European Communities "took into account" the relevant risk assessment techniques of the relevant international organizations as required by Article 5.1 of the *SPS Agreement* and, in paragraph 7.459, the Panel finds that it has.

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[255] EC's comments on interim report, para. 51.
[256] Panel Report on *Japan – Apples*, para. 8.241.

6.82 The European Communities asks the Panel to more fully summarize its arguments in paragraphs 7.474 and 7.475.[257] The Panel has, therefore, modified those paragraphs.

(iv) Assessment of the scientific arguments

6.83 The European Communities, argues that paragraphs 7.476-7.509 are incoherent and confused. Specifically, the European Communities believes that they do not adequately present the debate on the "threshold approach" which it believes is the central scientific debate.[258] The Panel notes that the content of paragraphs 7.476-7.509 contains the reasoning of the Panel on whether the Opinions satisfy the definition of a risk assessment set forth in Annex A(4) of the *SPS Agreement*. This section of the Panel's reasoning is not the appropriate place to present a debate between the parties about a particular scientific issue.

6.84 The Panel, however, is mindful that the parties did expend a significant amount of argument on the relevance of "thresholds" to the risk assessment process and that perhaps it would provide further clarity to include more explanation of the various arguments. Therefore, the Panel made modifications to the summaries of the parties' arguments. The Panel believes that the debate over the "threshold" issue can be divided into two main components. First, whether all four of the risk assessment steps as defined by Codex should be followed when the substance under review exhibits no threshold. Second, whether oestradiol-17β is such a substance that exhibits no threshold because it is genotoxic *in vivo* and therefore would lead to adverse effects even at the doses found in meat as a result of treatment of cattle with oestradiol-17β for growth promotion purposes.

6.85 The Panel also feels that it would be helpful to include some additional information provided by the experts with respect to this matter. Therefore, the Panel inserted a new paragraph after paragraph 7.454. The Panel also changed the first sentence of paragraph 7.457.

6.86 With respect to whether oestradiol-17β, in particular, is genotoxic *in vivo* and has no threshold, the Panel finds that the issue arises in two different contexts: first, in the context of what such a conclusion means for evaluating whether the SCVPH Opinions constitute a risk assessment within the meaning of the *SPS Agreement*; second, in the context of the analysis of whether the science supports the conclusions reached by the European Communities with respect to the genotoxic properties of oestradiol-17β. To address both of these issues the Panel edited paragraph 7.469.

6.87 The Panel also feels that it would be helpful to include some additional information provided by the experts with respect to this matter. Therefore, the Panel inserted a new paragraph after paragraph 7.501.

6.88 With respect to whether the science supports the conclusion that oestradiol-17β is a substance that exhibits no threshold, the Panel has added Dr. Cogliano's response to question 19 from the Panel[259] as paragraph 7.527.

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[257] EC's comments on interim report, para. 52.

[258] EC's comments on interim report, para. 53.

[259] Panel question 19, Annex D, p. 34 ("The European Communities states that '... it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance'. Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case), paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]")

6.89 The European Communities argues that paragraphs 7.487 and 7.488 of the interim report are a misinterpretation of what the Appellate Body found in the original *EC – Hormones* case about the concept of risk assessment and its significance in the *SPS Agreement*.[260] The European Communities does not provide any specific parts of the analysis that it feels are a misinterpretation, neither does it provide what it believes is the correct interpretation. The Panel can only assume that the European Communities maintains its position as summarized in paragraph 7.489.

6.90 The Panel based its reasoning in paragraphs 7.487 and 7.488 of the interim report on several passages in the Appellate Body Report on *EC – Hormones*. Paragraph 181 of the Appellate Body Report reads as follows:

> "The second preliminary consideration relates to the Panel's effort to distinguish between 'risk assessment' and 'risk management'. The Panel observed that an assessment of risk is, at least with respect to risks to human life and health, a 'scientific' examination of data and factual studies; it is not, in the view of the Panel, a 'policy' exercise involving social value judgments made by political bodies.[261] The Panel describes the latter as 'non-scientific' and as pertaining to 'risk management' rather than to 'risk assessment'.[262] We must stress, in this connection, that Article 5 and Annex A of the *SPS Agreement* speak of 'risk assessment' only and that the term 'risk management' is not to be found either in Article 5 or in any other provision of the *SPS Agreement*. Thus, the Panel's distinction, which it apparently employs to achieve or support what appears to be a restrictive notion of risk assessment, has no textual basis. The fundamental rule of treaty interpretation requires a treaty interpreter to read and interpret the words actually used by the agreement under examination, and not words which the interpreter may feel should have been used."

6.91 The Appellate Body disapproved of the panel's use in the original *EC – Hormones* dispute of the distinction between "risk assessment" and "risk management" because it had no textual basis. However, this did not mean that the Appellate Body endorsed an interpretation of Article 5.1 or Annex A(4) of the *SPS Agreement* that included a risk management stage. In fact, it emphatically stated that the term "risk management" is not to be found in Article 5 or any other provision of the *SPS Agreement.* The Panel, therefore, finds no basis for the European Communities' assertion that the Appellate Body confirmed that a risk assessment within the meaning of Article 5.1 includes "a risk management stage which to carry out is the responsibility of the regulator and not of the scientific bodies."[263]

6.92 This Panel, following the advice of the Appellate Body, has adhered strictly to the text of Article 5.1 and Annex A(4) of the *SPS Agreement* in its interpretation. In analysing the European Communities' compliance with Article 5.1 and Annex A(4) of the *SPS Agreement*, the Panel is also cognisant of the Appellate Body's finding that:

> "The listing in Article 5.2 begins with 'available scientific evidence'; this, however, is only the beginning. We note in this connection that the Panel states that, for purposes of the EC measures in dispute, a risk assessment required by Article 5.1 is 'a *scientific* process aimed at establishing the *scientific* basis for the sanitary measure a Member intends to take'.[264] To the extent that the Panel intended to refer to a process characterized by systematic, disciplined and objective enquiry and analysis, that is, a

[260] EC's comments on interim report, para. 55.
[261] (*footnote original*) US Panel Report, para. 8.94; Canada Panel Report, para. 8.97.
[262] (*footnote original*) US Panel Report, para. 8.95; Canada Panel Report, para. 8.98.
[263] EC's second written submission, para. 116.
[264] (*footnote original*) US Panel Report, para. 8.107; Canada Panel Report, para. 8.110.

> mode of studying and sorting out facts and opinions, the Panel's statement is unexceptionable.[265] However, to the extent that the Panel purports to exclude from the scope of a risk assessment in the sense of Article 5.1, all matters not susceptible of quantitative analysis by the empirical or experimental laboratory methods commonly associated with the physical sciences, we believe that the Panel is in error. Some of the kinds of factors listed in Article 5.2 such as 'relevant processes and production methods' and 'relevant inspection, sampling and testing methods' are not necessarily or wholly susceptible of investigation according to laboratory methods of, for example, biochemistry or pharmacology. Furthermore, there is nothing to indicate that the listing of factors that may be taken into account in a risk assessment of Article 5.2 was intended to be a closed list. It is essential to bear in mind that the risk that is to be evaluated in a risk assessment under Article 5.1 is not only risk ascertainable in a science laboratory operating under strictly controlled conditions, but also risk in human societies as they actually exist, in other words, the actual potential for adverse effects on human health in the real world where people live and work and die."[266]

6.93 Therefore, the Panel finds that a risk assessment consistent with Article 5.1 need not be limited to empirical or experimental laboratory methods commonly associated with the physical sciences. However, the Panel also agrees with the Appellate Body's statement that a requirement that a risk assessment be "a process characterized by systematic, disciplined and objective enquiry and analysis, that is, a mode of studying and sorting out facts and opinions" is unexceptionable.

6.94 Nowhere in the texts of Article 5.1 and Annex A(4) does the Panel find support for the European Communities' contention that a risk assessment within the meaning of the *SPS Agreement* includes "weighing policy alternatives in light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures."[267] What the European Communities seems to be describing is how a government chooses an appropriate SPS measure based on a risk assessment. The Panel does not find that this is contemplated by the texts of Article 5.1 and Annex A(4) of the *SPS Agreement*.

6.95 To avoid any confusion or misunderstanding the Panel modified paragraphs 7.490 through 7.492.

6.96 The Panel is aware that the experts responded to the Panel's questions with respect to what the European Communities had evaluated in its Opinions by using a terminology that is standard for risk assessments conducted according to the process outlined in the Codex Procedural Manual. Although the scientific experts' responses may include terms such as "hazard characterization" or "exposure assessment", the Panel is at all times aware that the relevant standard against which it is assessing the European Communities' measure is that of the *SPS Agreement*. In order to emphasize this point, the Panel added a new paragraph before paragraph 7.494.

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[265] (*footnote original*) "The ordinary meaning of 'scientific', as provided by dictionary definitions, includes of, relating to, or used in science', broadly, having or appearing to have an exact, objective, factual, systematic or methodological basis', of, relating to, or exhibiting the methods or principles of science' and of, pertaining to, using, or based on the methodology of science'. Dictionary definitions of science' include the observation, identification, description, experimental investigation, and theoretical explanation of natural phenomena', any methodological activity, discipline, or study', and knowledge attained through study or practice'". (footnotes omitted) *United States' Statement of Administrative Action, Uruguay Round Agreements Act*, 203d Congress, 2d Session, House Document 103-316, Vol. 1, 27 September 1994, p. 90.

[266] Appellate Body Report on *EC – Hormones*, para. 187.

[267] EC's reply to question 24 of the Panel after the first substantive meeting, Annex B-1, para. 137.

6.97 The European Communities takes issue with the reliance of the Panel on certain statements by the experts in paragraphs 7.494-7.500 and cites to various other statements by the same experts which it claims stand for the opposite proposition.[268] The Panel takes note that Annex D, which contains the replies of the experts to the Panel's questions is 116 pages long and Annex G which contains the transcript of the Panel's meeting with the experts is 170 pages long. This does not include the various comments and comments on comments of the parties on the experts' responses and on the transcripts. With this volume of information, every comment by the experts could not be included in the Panel findings and, for that matter, did not have to be.[269] Therefore, the Panel made a decision to select quotations that are representative of a particular expert's opinion on a given topic. The Panel has reviewed the specific paragraphs referred to by the European Communities in an attempt to determine if it misunderstood or misrepresented a particular expert's opinion.

6.98 With respect to Dr. Guttenplan, the European Communities objects to the Panel's reliance on paragraph 145 of the experts replies to the Panel's questions and refers the Panel to paragraphs 366, 393, 713, and 716-718 of Annex G as well as his written reply to Panel question 17 which is at paragraph 176 of Annex D.[270]

6.99 With respect to the Panel's reliance on paragraph 145 of Annex D, which is Dr. Guttenplan's response to Panel question 13, cited in paragraph 7.495, the Panel amended the paragraph to better reflect Dr. Guttenplan's complete response to the question.

6.100 Additionally, to more fully reflect Dr. Guttenplan's written answer to question 52 of the Panel, the Panel modified paragraph 7.500.

6.101 With respect to Dr. Guttenplan's other interventions cited by the European Communities, the Panel did not deem it necessary to make any additional changes in this section.

6.102 Paragraph 366 of Annex G refers to Dr. Guttenplan's opinion that oestrogen is genotoxic, but that it may not be possible to "really estimate the risk at this point from such low levels of genotoxic effects."[271] Paragraph 393 of Annex G refers generally to the issue of conducting risk assessments of genotoxic substances with no threshold.[272] The Panel believes it has dealt with these issues in the amendments mentioned above.

6.103 Paragraphs 713 and 716-718 of Annex G reflect Dr. Guttenplan's opinion that although, because anything is possible, there may be a risk from consumption of meat derived from cattle treated with oestradiol-17β for growth promotion purposes, it is so low that it is not susceptible to calculation. It also reflects an interjection by the European Communities asking Dr. Guttenplan to confirm his statement that, although the risk is small and cannot be evaluated or calculated, it is not zero.

6.104 The Panel does not believe that these statements are directly relevant to the Panel's reasoning on whether the European Communities conducted a risk assessment consistent with the definition set forth in Annex A(4) of the *SPS Agreement*. As the Panel has noted, the purpose of the risk assessment is to evaluate the possibility that an identified adverse effect comes into being, originates, or results from the presence of the identified additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs. It is not to guarantee that said possibility will be below the Member's appropriate level of protection or indeed will be zero.

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[268] EC's comments on interim report, para. 56.
[269] Appellate Body Report on *EC – Hormones*, para. 138; see also Section VII.C.3.(d)(iii) of this report.
[270] EC's comments on interim report, para. 56.
[271] Transcript of the Panel meeting with the experts, Annex G, para. 366.
[272] Transcript of the Panel meeting with the experts, Annex G, para. 393.

6.105 Finally, the European Communities cites Dr. Guttenplan's written response to question 17 of the Panel. In that paragraph, Dr. Guttenplan states that the absence of catechol metabolites in meat from treated animals does not imply that the meat is without risk for genotoxicity. Dr. Guttenplan was being asked to evaluate a particular argument by Canada. The Panel does not read this statement as implying that the residues of oestradiol-17β in meat from treated cattle are definitely genotoxic. However, even if this were the case, the issue of genotoxicity is only relevant to the issue of whether a threshold could be determined for this substance. Again, the Panel believes it has addressed this point with the additions and edits suggested above.

6.106 The European Communities also refers the Panel to various interventions by Dr. Cogliano at the Panel meeting with the experts, namely, paragraphs 400, 404, 406, 409, 870, and 1021-1025 of Annex G.[273] In paragraphs 400, 404, and 406 of Annex G, Dr. Cogliano provides the Panel with general background information on the issue of thresholds and linear dose response curves. The comments are not specific to the Opinions of the European Communities and therefore are not relevant to the analysis the Panel is undertaking in this particular section. Paragraph 409 of Annex G contains a question from the Chairman. The Panel is unsure whether the European Communities meant to refer to paragraph 408 or paragraph 410.[274] In any event, in both those paragraphs Dr. Cogliano provides general background information on what is meant by a linear dose response curve.

6.107 Dr. Cogliano, in paragraph 871 of Annex G[275], states that the data are not sufficient to conduct a "JECFA-style" risk assessment if oestradiol-17β has no threshold. The Panel finds this statement unremarkable for two reasons. First, the Panel is not evaluating whether the European Communities has done a "JECFA-style" risk assessment, but whether it has done a risk assessment consistent with the definition set forth in Annex A(4) of the *SPS Agreement*. Second, the European Communities has not argued that there is insufficient data to conduct a risk assessment of oestradiol-17β, it has argued that it has conducted a risk assessment of oestradiol-17β that is consistent with the *SPS Agreement*, that its measure is based on that risk assessment and that, consequently, it has acted consistently with Article 5.1 of the *SPS Agreement*. Dr. Cogliano's statement, in the paragraph cited by the European Communities, is not directly relevant in this context.

6.108 Paragraphs 1021 through 1025 of the transcript of the panel meeting with the experts report a discussion where both Drs. Boobis and Cogliano confirm that the fundamental difference between the JECFA study and the SCVPH Opinions is the willingness to assume a threshold and interpret the data from that standpoint. The Panel has now cited these interventions in the new paragraphs 7.455-7.456 and paragraph 7.502.

6.109 In its comments on the interim report, the European Communities argues that if the Panel had properly looked at Dr. Cogliano's interventions in these paragraphs of the transcript the Panel would have had to conclude that the European Communities' risk assessment has followed one side of a legitimate debate while JECFA has followed another.[276] The European Communities seems to imply that if the Panel recognizes this it would also conclude that the European Communities' ban on the importation of meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes was based on a risk assessment within the meaning of Article 5.1 and Annex A(4) of the

[273] EC's comments on interim report, paras. 56-58.

[274] Because the specific paragraph references by the European Communities in its comments on the interim report frequently tend to differ from the version in Annex G, the Panel believes that the European Communities must have prepared its interim comments with a different version of the transcript than the one contained in Annex G. In each instance of mistaken citation, the Panel has read the paragraphs in the transcript surrounding those cited by the European Communities to ensure that it has correctly identified and is responding to the concerns expressed by the European Communities.

[275] Paragraph 870 is the Chairman giving the floor to Dr. Cogliano.

[276] EC's comments on interim report, paras. 57-64.

SPS Agreement. The Panel does not see the issue in quite the same manner as the European Communities. The issue is not whether a risk assessment following the four steps as defined by Codex could or should have been completed. The issue is whether the European Communities has conducted a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*.

6.110 The Panel does not take a position on the science or on how to evaluate data when a particular substance exhibits no threshold.[277] However, whatever approach the European Communities adopts in its assessment of the risks, it is obligated to conduct a risk assessment that is consistent with the definition set forth in Annex A(4) of the *SPS Agreement*. The Panel finds that the *SPS Agreement* requires an analysis that goes beyond the identification of a potential adverse effect. The analysis must include an examination of the potential for that adverse affect to come into being, originate, or result from the presence of the specific substance under review in food, beverages, or feedstuffs, in this case oestradiol-17β in meat and meat products derived from cattle treated with the hormone for growth promotion purposes. The Panel will not prescribe a particular manner or approach for how the analysis should be conducted, but the analysis must be conducted.

6.111 The intervention by Dr. Sippell in paragraph 576 of Annex G cited by the European Communities mentions a scientific study cited in the 1999 Opinion which posits that the radioimmuno assays originally used to calculate daily endogenous production levels of the hormones may have overestimated these levels. The Panel addressed this issue by inserting in paragraph 7.507 quotations from the 1999 SCVPH Opinion on this issue directly, and a new paragraph 7.508.

6.112 Additionally, the Panel felt that more direct quotation from the Opinions with respect to the other identified potential adverse effects would provide greater clarity. Therefore, the Panel modified paragraphs 7.506 and 7.507.

6.113 The European Communities also refers to a statement by Dr. Boobis at paragraph 725 of Annex G. [278] The Panel has reviewed the surrounding paragraphs and found that, like Dr. Guttenplan, Dr. Boobis had engaged in an exchange with the European Communities about the concept of zero risk. Again, Dr. Boobis confirms that science cannot provide absolute assurance of the absence of risk or an absolute guarantee of safety. Dr. Boobis also states "it is not clear to me how you would ever conduct a risk assessment and guarantee that, without ensuring zero exposure, and of course that would cease all use of all compounds where there is any risk whatsoever, and they all have some risk."[279]

6.114 As with the citations to Dr. Guttenplan's statements at the meeting with the Panel, the Panel is unclear what the European Communities believes this reference to certain statements by Dr. Boobis will add to the Panel's reasoning on whether it conducted a risk assessment consistent with the definition set forth in Annex A(4) of the *SPS Agreement*. The Panel notes again that the purpose of a risk assessment is to evaluate the possibility that an identified adverse effect comes into being, originates, or results from the presence of the identified additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs, not to guarantee that said possibility will be below a Member's appropriate level of protection or indeed will be zero.[280]

[277] EC's comments on interim report, para. 78. Contrary to the assertion of the European Communities, the Panel does not endorse any one particular way to approach risk assessment.

[278] Paragraph 725 is an interjection by Canada. See transcript of the Panel meeting with the experts, Annex G, para. 725.

[279] Transcript of the Panel meeting with the experts, Annex G, paras. 723 and 729.

[280] The Panel notes that the Appellate Body in para. 186 of its report on *EC – Hormones*, asked "if a risk is not ascertainable, how does a Member ever know or demonstrate that it exists?"

6.115 The European Communities argues that in paragraphs 7.525-7.534 the Panel relies solely on the responses of Drs. Boobis and Boisseau and does not reflect the opinions of the other experts.[281]

6.116 The Panel notes that the relevant section is from paragraphs 7.520-7.540 and that the Panel cites Dr. Cogliano and Dr. Guttenplan in paragraph 7.536 and Dr. Guttenplan again in paragraph 7.537. Nevertheless, the Panel has examined the written answers of the other experts to the same questions of the Panel as well as the transcript of the Panel meeting with the experts and made additional references to experts' statements.

6.117 The European Communities argues that the Panel is in error in paragraph 7.538 when it states that the only study cited with respect to susceptible populations was one having to do with *in utero* exposure to DES, which is banned in the United States.[282] The Panel has reviewed the paragraphs in the 1999 Opinion referenced by the European Communities. Although the European Communities is correct that other studies regarding susceptible populations are referenced in section 2.2.2.4 entitled "Potential adverse effects of exogenous sex hormones on growth and puberty upon exposure of prepubertal children," the Panel, in paragraph 7.538, was specifically referring to the link between *cancer* and consumption of hormone treated meat. With respect to that specific identified potential adverse effect, the only study mentioned in section 2.3.2.4 under susceptible populations with respect to oestrogen is one involving *in utero* exposure to DES. The Panel modified the third sentence of paragraph 7.538.

6.118 Additionally, based on the European Communities' comment, the Panel also reviewed the paragraphs in the interim report which dealt with section 2.2.2.4 of the 1999 Opinion. In order to ensure that the Panel fully reflects the science the European Communities relied upon in this section, the Panel amended paragraph 7.505.

6.119 The European Communities argues with respect to paragraph 7.540 that, because the Panel based its findings on the views expressed by the "most convincing" experts, the Panel has failed to make an objective assessment of the matter, failed to take properly into account the totality of the available evidence and failed to give proper weight to different scientific views which are based on genuine and legitimate scientific grounds. The European Communities also argues that the Panel's "most convincing" experts are the ones it had alleged had a conflict of interest.

6.120 The Panel bases its analysis in this section on its own reading of the plain language in the Opinions which was corroborated by the views expressed by the experts and this combination leads the Panel to its conclusions. Additionally, the Panel disagrees with the European Communities that it fails to examine the totality of the evidence or to give proper weight to particular scientific views. As the Panel notes, it does not disregard any of the statements by the experts. However, the Panel could not possibly provide full quotations of every answer or statement of every expert. The fact that the Panel may have cited specific passages from specific experts does not mean that the Panel did not consider and weigh all of the responses.

6.121 The Panel, after reading the Opinions, the experts' answers to questions, the transcript of the meeting with the experts, and the parties submissions and comments, made a determination about which experts had provided the Panel with answers that responded to the questions asked in a clear and consistent manner supported by expertise and evidence. This determination is the essence of weighing the evidence. As the Panel noted above, in paragraphs 7.520-7.540, the section to which paragraph 7.540 belongs, the Panel cited Dr. Boisseau, Dr. Boobis, Dr. Cogliano, and Dr. Guttenplan. These are the experts who answered the relevant questions and who had identified expertise in risk

[281] EC's comments on interim report, footnote 11.
[282] EC's comments on interim report, footnote 11.

assessment, toxicology, studies of carcinogens, and biochemistry.[283] The Panel regrets if it caused any confusion by using the phrase "most convincing" and accordingly clarified paragraph 7.540.

6.122 The European Communities fails to see why the Panel, after having concluded that there is no risk assessment, goes on to examine whether the science supports the conclusions in the Opinions and asks for more explanation than previously provided for. The Panel modified paragraph 7.510 in order to provide additional explanation.

(v) Comments on the Panel analysis regarding the other five hormonal substances

6.123 The European Communities argues that paragraph 7.583 is unclear and seems irrelevant for the further analysis of the Panel. The European Communities first argues that, in its oral statement, it spoke about whether a risk assessment can reach a definitive conclusion, not whether or not it is possible to perform a definitive risk assessment. First, the Panel recalls that the EC reference to a "definitive risk assessment" is found in the EC second written submission.[284] Second, the Panel does not see any real difference between "reach[ing] a definitive conclusion" and making a "definitive risk assessment". Its reasoning in paragraph 7.583 thus applies equally to both statements.

6.124 Second, the European Communities considers that the Panel should have referred to what the experts said at the hearing about the issue of whether scientific data can ever allow for a definitive conclusion to be reached. This seems to suggest that the European Communities no longer argues that what matters in order to justify the application of Article 5.7 is whether a definitive conclusion can be reached or whether a definitive risk assessment can be made. If this is correct, the Panel does not believe that it is entitled to address new arguments at the interim review stage. The Panel nevertheless reviewed the comments of Dr. Cogliano referred to by the European Communities. In paragraph 776 of Annex G, Dr. Cogliano suggests that there can be different types of risk assessments, depending on the specificity of the risk one wishes to identify. The Panel fails to see in what respect this statement affects its finding in paragraph 7.583. As recalled by the Panel in its findings[285], the type of risk assessment requested under Article 5.1 is a risk assessment within the meaning of Annex A(4) of the *SPS Agreement*, which is not one of the types of risk assessment identified by Dr. Cogliano. It is in the context of the completion of a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement* that the Panel discussed the EC argument regarding a "definitive risk assessment" or a "risk assessment reach[ing] a definitive conclusion". The other comment of Dr. Cogliano referred to by the European Communities[286] suggests that data may be sufficient to do one type of risk assessment (e.g. "the JECFA-style ADI") but not one based on a theory according to which it is not possible to identify a dose below which there is no risk, because there is a risk at any dose level, even the low doses one might find in hormone-treated meat. The Panel notes in this regard that this is different from arguing that one should be able to invoke Article 5.7 because one cannot make a "definitive risk assessment". As mentioned by the Panel, the Appellate Body in *Japan – Apples* did not say that relevant scientific evidence would become insufficient if a Member could not perform a particular type of risk assessment, but only if it would be unable to perform a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*.

6.125 The Panel did not deem it necessary to delete or modify paragraph 7.583.

6.126 The European Communities makes a general reference to its second written submission and takes issue with the assessment of the Panel in paragraphs 7.627-7.698 by stating that the Panel did

[283] Transcript of the Panel meeting with the experts, Annex G, paras. 54-72.
[284] *Inter alia* in paras. 137 and 143.
[285] See paras. 7.432-7.433.
[286] Annex G, para. 871.

not properly and fully examine the reasons contained in the Opinions and relied exclusively on certain statements of a minority of the experts it had chosen to advise it, while ignoring pertinent statements of the other experts. The Panel notes that it addressed the EC comments on its findings where they were directed at precise aspects of the interim report. This was the case regarding comments on the Panel's reliance on the views expressed by some of the experts it consulted and for comments regarding the existence of sufficient relevant scientific evidence. The Panel does not deem it necessary to address those issues in general terms here.

6.127 The European Communities finds the Panel reference to a risk assessment "in substance" in paragraph 7.606 to be "entirely unclear". In the opinion of the Panel, one can always follow each of the Codex steps provided for the gathering and analysis of scientific evidence. However, in order to be a risk assessment within the meaning of Article 5.1, that exercise must reach scientific conclusions that are supported by the scientific evidence therein.[287] Thus, the possibility to complete a risk assessment depends on whether the relevant scientific evidence is sufficient to support a conclusion on whether the identified adverse effect arises from, comes into being, or occurs as a result of the presence of the substance at issue in food, beverages, or feedstuffs.

6.128 The European Communities seems to suggest, in substance, that whether a risk assessment can be completed depends on the level of protection chosen by a given Member. The European Communities seems to link the conduct of the risk assessment with the desired outcome of a given SPS measure; i.e. to ensure zero risk. The Panel believes that this is not what the *SPS Agreement* requires. The Panel considers that the European Communities' interpretation is not supported by the text of Article 5.7, which only refers to the insufficiency of relevant scientific evidence. There is no indication that this insufficiency is to be assessed in relation to the Member's level of protection. Otherwise the negotiators would have stated "in cases where relevant scientific evidence is insufficient in the light of the level of protection chosen by the Member adopting of maintaining a sanitary measure". Nothing in the context of Article 5.7 suggests this interpretation either. Articles 2.2, 3.3 and 5.1 provide relevant contextual support for the proposition that the purpose of the *SPS Agreement* was to ensure that Member's SPS measures are "objectively justified"[288] by science. This purpose would be defeated if a Member could invoke Article 5.7 whenever relevant scientific evidence is insufficient to objectively justify the type of measure that would achieve a particular desired level of protection. The Panel modified paragraph 7.606 in order to clarify what it meant.

6.129 Regarding paragraphs 7.608-7.615, the European Communities argues that the Panel's discussion does not do justice to the role genuine scientific uncertainty plays in risk assessment. It contests the Panel's exclusive reliance on the opinions of Dr. Boisseau and Dr. Boobis and refers to statements by experts other than those quoted by the Panel. As far as the Panel's reliance on Dr. Boisseau and Dr. Boobis is concerned, it should be recalled that this is a risk assessment issue and these two scientists were selected by the Panel *inter alia* because of their expertise on risk assessment. Yet, Dr. Boisseau and Dr. Boobis were not the only ones with the same view. Dr. Tritscher's remarks on the subject also support the Panel's conclusion.[289]

6.130 None of the interventions of experts cited by the European Communities in its comments contradicts the conclusions reached by the Panel in its interim report, which are clearly spelled out in paragraph 7.615. More particularly, none of Dr. Cogliano's statements cited by the European Communities contradicts the Panel. In the paragraphs cited by the European Communities, Dr. Cogliano mainly explains the role of IARC and whether there is uncertainly about genotoxicity. Similarly, in the paragraphs cited by the European Communities, Dr. Guttenplan says that there is uncertainty about certain scientific issues, but he does not address the role of uncertainty in risk

[287] Panel Report on *Japan – Apples (Article 21.5 – US)*, para. 8.136.
[288] Appellate Body Report on *EC – Hormones*, para. 190.
[289] Annex G, para. 348.

assessment. Dr. Sippell addresses an issue unrelated to risk assessment. Dr. De Brabander addresses the quality of data and improved methods. Regarding the alleged misinterpretation of some of the statements of Dr. Boobis on the existence or not of genuine scientific uncertainty, it seems that the paragraph referred to by the European Communities (Annex G, paragraph 1049) deals with a different issue: that of scientific uncertainty in relation to U-shaped dose-response curves, not how scientific uncertainty is treated in risk assessment.

6.131 The European Communities argues, with respect to paragraph 7.622**,** that the risk assessments performed by JECFA do not contain the specific evidence that the Panel allegedly found to be missing in the EC Opinions and, therefore, cannot constitute proper risk assessments. The Panel notes that there is no reference to the JECFA risk assessment of oestradiol-17β in the Panel's analysis of the consistency of the European Communities' permanent ban on meat and meat products derived from cattle treated with oestradiol-17β for growth promotion purposes, because the European Communities claimed that it completed its own risk assessment for oestradiol-17β. The Panel thus conducted an analysis of the SCVPH Opinions and sought to determine whether they complied with the definition of a risk assessment in Annex A(4) and whether the science contained therein supported the European Communities' decision to institute a total ban. Unlike the analysis under Article 5.7, with respect to oestradiol-17β the Panel was not trying to determine whether there was sufficient scientific information to conduct a risk assessment. The Panel recalls that the fault it found with the Opinions was not that any particular piece of evidence was missing, but rather that the Opinions did not specifically analyse the risk of the identified adverse effects *arising from* the presence of oestradiol-17β in food, beverages, or feedstuffs. Therefore, whether JECFA relied on the same evidence as the European Communities in its analysis of oestradiol-17β is irrelevant. The Panel notes that JECFA did take into account the dose levels in meat and meat products and attempted to calculate the risk to humans from consuming typical amounts of meat. JECFA used a series of assumptions regarding meat consumption, circulating levels of oestrogen in the blood for various sub-groups of the population, etc. The European Communities may very well be right that there are other ways to analyse the risk than those JECFA utilized. The Panel does not take a position on that issue. What the Panel has said, is that such an analysis is required by Article 5.1 and Annex A(4) of the *SPS Agreement*.

6.132 With respect to the Panel's reference to the concept of "critical mass" in paragraph 7.626, the European Communities request that we provide an explanation of where this criterion comes from and whether it is in conformity with the findings of the Appellate Body in *EC – Hormones*.

6.133 The Panel used the term "critical mass" in full knowledge of its meaning.[290] It used it in the sense of a situation where evidence becomes quantitatively and qualitatively sufficient to call into question the fundamental precepts of previous knowledge and evidence. The Panel does not mean that there must be sufficient evidence to perform a new risk assessment. Otherwise, Article 5.7 of the *SPS Agreement* would become meaningless. It used the term "critical mass" very much in its common scientific usage, i.e. the new scientific information and evidence must be such that they are *at the origin* of a change in the understanding of a scientific issue. We do not see in what respect this approach by the Panel, which applies to the specific situation in this case (i.e. one where a party alleges that previously sufficient scientific evidence has become insufficient) would be contrary to the findings of the Appellate Body in *EC – Hormones.*

[290] In mathematics and physics "critical" is defined as "constituting or relating to a point of transition from one state, etc. to another. "Critical size" or "critical mass" are defined as the minimum size or mass of a body of a given fissile material which is capable of sustaining a nuclear chain reaction (Shorter Oxford English Dictionary, 5th edition (1993), p. 558). In other words, the Panel assessed whether it had been provided with the minimum evidence necessary to conclude that knowledge has become quantitatively and qualitatively sufficient to call into question the fundamental precepts of previous knowledge and evidence.

6.134 The European Communities takes issue with paragraph 7.640. The European Communities contests the Panel's approach in defining a list of general issues common to all five hormones. The European Communities argues that it has identified exactly, for each hormonal substance, the sections in the 1999 Opinion that deals individually with that substance and suggests that the Panel's list of "general issues" common to all five hormones is arbitrary.

6.135 The Panel first recalls that, as a general principle, panels are free to structure the order of their analysis as they see fit.[291] The Panel does not deny that the EC Opinions addressed each hormone individually. However, as explained in paragraphs 7.637-7.639, some issues were common to all five hormones and the evidence provided was not always sufficiently specific to address a particular issue in relation to each hormone individually. The Panel modified paragraphs 7.629-7.640 and the title to Section VII.C.3.(f)(vi) to reflect the fact that what is discussed are issues common to all hormones for which hormone-specific evidence was not provided.

6.136 The Panel also clarified that certain insufficiencies identified in the EC Opinions had not as such been discussed by the European Communities in its submissions. The Panel concluded that the European Communities was not arguing that these particular insufficiencies were what made it impossible to complete a risk assessment. Therefore, the Panel decided not to address these insufficiencies. This may have prompted the EC comment that the Panel analysis on the individual hormonal substances in paragraphs 7.699-7.816 was incomplete. The clarification brought by the Panel demonstrates that it did not draw a random list of issues common to all hormones and explains the reasons why a more limited number of issues was discussed compared with what had been identified in the Opinions. The Panel has also clarified this point in the sections relating to each hormone individually and did not follow the request of the European Communities that it address each and every issue of insufficiency raised in the Opinions.[292]

6.137 The European Communities contests the conclusions of the Panel in paragraph 7.642**,** footnote 739 as inaccurate, but without specifying why. In that footnote, the Panel refers to a new method and new assays to detect small amounts of hormones in meat, mentioned in the 2002 Opinion. From what is mentioned in the 2002 Opinion, the studies were on the subject of hormone levels in meat, not in people. Whereas it might be possible to apply these method and assays to detect endogenous levels of hormones in humans, the European Communities does not argue this in its comments, and this is not what the method and assays are about. It also appears that, according to the 2002 Opinion, the method and assays mentioned were not exactly successful or trustworthy. The conclusion in section 4.1.1 of the 2002 Opinion, where the new method is discussed, reads: "[D]espite a number of positive analytical results in this study, the low number of samples does not allow a qualified validation of typical characteristics such as sensitivity, specificity, accuracy and reproductibility." (2002 Opinion, page 9). The conclusion of section 4.1.2, where the bioassays are discussed, is that: " [T]he obtained results suggest that the use of recombinant yeast and rainbow trout hepatocytes to detect oestrogenic compounds is not justified in view of their lack of sensitivity". (2002 Opinion, page 9). It seems that, even if they were relevant in the context of paragraph 7.642 this new method and assays do not contribute to a critical mass of evidence that would put into question existing knowledge. The Panel, therefore, did not modify footnote 739.

6.138 With respect to paragraphs 7.644-7.647, the European Communities argues that the Panel reduces the discussion to only two quotations and draws a conclusion that is not based on the debate with the experts at the hearing. The European Communities argues that "much more was said about this issue" at that hearing.[293] The Panel notes, however, that the discussion related to the sensitivity of children to hormones in general, without drawing any direct link with any of the five hormones at

[291] Appellate Body Report on *Canada – Wheat Exports and Grain Imports*, para. 126.
[292] EC's comments on Sections VII.C.3(f)(vii), (viii), (ix), (x), (xi).
[293] Annex G, para. 561 *et seq*.

issue in this section, and to the validation of methods, particularly of the new ultrasensitive assay (the "Klein" methodology). The only hormone expressly discussed in relation to this assay was oestradiol-17β. The Panel notes that it concludes in this section that (a) the studies using the new ultrasensitive assay were limited to oestradiol-17β; and (b) that the ultrasensitive assay had not been validated. Thus, the Panel does not agree with the European Communities that its conclusions are not based on the debate referred to above.

6.139 The European Communities requests that we clarify the first sentence in paragraph 7.647. More particularly, the European Communities requests that we specify whether this is a legal argument or a scientific argument. The Panel considers that the finding that the evidence relates only to oestradiol is not an argument but a factual consideration. The Panel considers that, since the new detection method measured oestradiol only[294] and since no evidence was provided that suggested that extrapolation had been made or could be made to other hormones, the evidence is insufficient to conclude, with respect to the five hormones subject to a provisional ban under Article 5.7 of the *SPS Agreement*, that existing knowledge has been put into question.

6.140 With respect to the EC comment on the second sentence of paragraph 7.647, the Panel confirms that, indeed, its understanding is that the ultrasensitive detection method used by Klein and subsequently relates only to oestradiol and has not been validated. This has been confirmed by Dr. Boobis at the hearing.[295] As a result, the Panel cannot conclude that existing knowledge and evidence have been put into question by the results of the ultrasensitive assay with regard to the impact of the five hormones on prepubertal children if the available evidence relates only to oestradiol.

6.141 Even if the ultrasensitive assay had been validated and had demonstrated lower levels of the five hormones at issue in this section – and not only oestradiol – in sensitive populations, the Panel notes that the 1999 Opinion itself states that "[A] corollary is that perhaps the hormones residues in beef, which are also low and which have also been determined by RIA are equally variable and over representative of the actual hormone concentrations."[296]

6.142 In its comments regarding paragraphs 7.649-7.652 the European Communities considers that the Panel's approach to the issue of dose response is flawed and circular.

6.143 The European Communities bases its contention that the Panel's reasoning is circular on the assumption that the Panel rejected the EC approach based on an absence of a dose response analysis. Even though it rejected that approach in this particular case for oestradiol-17β, the Panel did not exclude that there could be situations where dose response would not apply. The Panel believes, on the contrary, that it is the European Communities that is making contradictory arguments. The European Communities cannot argue that "the Appellate Body clearly judged that a risk assessment [could] be either qualitative or quantitative"[297] and that a dose response is not *required* in order to complete a risk assessment and, at the same time, argue for the five hormones at issue that relevant scientific evidence is insufficient to perform a risk assessment because the data available do not allow a dose response assessment. Yet, this is what appears to be concluded in the 1999 Opinion as far as the five hormones are concerned. The Panel nonetheless clarified the paragraphs at issue.

6.144 The European Communities argues that, in paragraph 7.654, the Panel declines to discuss bioavailability on the basis that the studies relied upon by the European Communities do not relate to the five hormones in question, but only to oestradiol and that there is no indication that the

[294] See para. 7.645 quoting Dr. Sippell. See, also, Dr. Sippell's statement in Annex G, para. 588.
[295] Annex G, para. 572.
[296] 1999 Opinion, section 3.2, p. 30.
[297] See EC's reply to question 26 of the first series of questions of the Panel, para. 153, Annex B.

conclusions can be applied to hormones other than oestrogens. The European Communities considers that this assertion by the Panel is without foundation.

6.145 In order to reach its conclusion, the Panel examined most particularly the portions of the 1999 and 2002 Opinions quoted by the European Communities in its reply to question 28 of the questions of the Panel after the first substantive meeting[298] and in its second written submission.[299] The two extracts quoted by the European Communities address only oestradiol, while making references to oestrogens. Furthermore, the extract of the 1999 Opinion quoted by the European Communities is part of the section of the Opinion regarding oestradiol. The Panel notes that the European Communities argued that "similar findings [had been] made for all the other five hormones."[300] However, the European Communities did not specify where such findings had been made. This allegation has to be considered in relation to the comments of the experts. The Panel nonetheless deemed it necessary to clarify the section on bioavailability.

6.146 In its comments on the interim report, the European Communities also refers to the experts' replies to question 43. The Panel first notes that this question concerns bioavailability in general, not the sufficiency of evidence regarding bioavailability. The Panel has included quotations of the relevant passages of the experts' replies in its findings. The European Communities also refers to paragraphs 132 *et seq.* of the transcript of the hearing (Annex G). The Panel reviewed the comments of the experts on bioavailability and found that those comments address neither the bioavailability of the five hormones at issue, nor the sufficiency or insufficiency of evidence on it.

6.147 With respect to paragraphs 7.662 to 7.677, the European Communities argues first that the discussion on long latency of cancer and confounding factors should have been in the Panel's analysis under Article 5.1 of the *SPS Agreement*. We note that the Panel addressed this question to the extent this was necessary for its analysis under Article 5.1. The question of the latency period of cancer and of the epidemiological survey of the occurrence of cancer in various populations was addressed in paragraphs 7.535 *et seq.* The Panel also deemed it necessary to address the latency of cancer in its section under Article 5.7 because the European Communities argued that the long latency period of cancer made it impossible to demonstrate positively the existence of clear harm in relation to the hormones at issue. The Panel first determined whether long latency of cancer was relevant for the performance of a risk assessment for the hormones at issue. It then proceeded to determine whether relevant scientific evidence in relation to the latency of cancer was insufficient to the point of making it impossible to perform a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*. In order to do this, it assessed whether it could be considered that a "critical mass" of new information or evidence was now available which could unsettle the way long latency of cancer has been taken into account in risk assessment so far. The Panel clarified the part of Section VII.C.3.(f)(vi) dealing with long latency of cancer and confounding factors in order to better present its analysis.

6.148 The European Communities also argues that the section on long latency of cancer and confounding factors is evidence that we applied a "double standard" of evidence for the removal as compared to the approval of the hormones at issue. We did not argue that JECFA or the respondent performed the epidemiological studies necessary to demonstrate an absence of long term effect of the hormones at issue in terms of cancer. We note that the long latency of cancer has been acknowledged. We also note that confounding factors make it difficult to assign a particular cancer to specific circumstances of ingestion of hormone residues. We recall that JECFA's risk assessments take into account the long latency of cancer through the ADI. To the extent that the European

[298] Annex B-1, paras. 155-159.
[299] Paras. 131-166.
[300] EC's reply to question 28 of the questions of the Panel after the first substantive meeting, Annex B-1, para. 158.

Communities disagrees with the approach followed by JECFA, it is for the European Communities to provide a "critical mass" of evidence – not a "positive evidence" – that this approach is no longer valid.[301] We conclude that, in these proceedings, the European Communities has not pointed at evidence suggesting that long latency of cancer has not been appropriately taken into account in existing risk assessments.

6.149 The European Communities also takes issue with the Panel's discussion on the immunological effect of the five hormones in paragraphs 7.678-7.685. The European Communities seems to raise two issues in its comments. The first one is related to the question of whether a threshold approach must be followed. The second one is whether the Panel dismissed the EC arguments on the basis that the scientific evidence relates to oestrogens only.

6.150 Regarding the first issue, the Panel notes that all three experts who answered question 59[302] stated that there is no evidence of effects on the immune system from doses such as those resulting from consumption of meat from treated animals. If the point the European Communities wishes to make in its comments is that the approach based on a "threshold" is not required to assess the effect of the five hormones at issue on the immune system, then the Panel fails to understand why, under those circumstances, the relevant scientific evidence on the effect of the five hormones on the immune system is insufficient for the European Communities to perform a risk assessment for those hormones.

6.151 With respect to the second issue, the Panel notes that Dr. Boobis and Dr. Guttenplan address the effect of oestrogen/oestradiol on the immune system (Dr. Boobis refers to "hormones such as oestradiol"). As the Panel mentions in paragraph 7.681, the main reason for dismissing the EC arguments on insufficiency of evidence regarding the effect of hormones on the immune system is the fact that the evidence made available to the Panel relates exclusively to the effect of oestrogens. The European Communities has not identified any evidence that specifically addresses any of the five hormones at issue in this section. The European Communities has not explained either to the Panel why it thinks the evidence on oestrogens would be relevant for the other hormones. The Panel notes in this respect that the Opinions do not identify any evidence with respect to the five hormones that residue levels in meat might have an effect on the immune system. The Panel nonetheless clarified paragraphs 7.683-7.684.

6.152 Regarding paragraphs 7.686-7.698, the European Communities argues that the Panel quotes Dr. Sippell as identifying adverse effects, but does not discuss his statement. The European Communities adds that there is also no discussion of the other experts' views put forward at the hearing.

6.153 Regarding Dr. Sippell's statement in paragraph 7.691, the Panel has further discussed the points raised by the experts on this matter in paragraphs 7.692 through 7.698.

6.154 With respect to paragraphs 7.674 to 7.687 of the interim report, the European Communities argues that the Panel's discussion of the potential misuse and abuse in the administration of hormones is in the wrong place, to the extent that this is an aspect of risk assessment, in the sense of Article 5.1 to 5.3 of the *SPS Agreement*, that is applicable across all identified potential risks and for all six hormones. The Panel agrees with the European Communities that the question of misuse and abuse in the administration of hormones may apply to all six hormones at issue and is an element that can be taken into account in risk assessment, as set forth in Article 5.2 of the *SPS Agreement* and confirmed by the Appellate Body in *EC – Hormones*. However, the Panel did not deem it necessary to address this question in the section regarding the conformity with Article 5.1 of the definitive ban on

[301] In this respect, the Panel inserted a footnote in para. 7.626 to address the EC argument on standard of proof.

[302] Annex D, paras. 443-448.

oestradiol-17β, to the extent that the question whether misuse or abuse exists in the administration of hormones did not have an impact on the issues addressed by the Panel under Article 5.1. Indeed, the question of misuse or abuse in the administration of hormones is relevant to the extent that it can lead to higher concentrations of hormone residues in meat and meat products than would occur if good veterinary practices are applied. As stated by the 1999 Opinion, it is an aspect of exposure assessment. In this case, the Panel found that the European Communities had not evaluated specifically the possibility that the adverse effect that it had identified in its risk assessment come into being, originate, or result from the consumption of meat or meat products which contain veterinary residues of oestradiol-17β as a result of the cattle being treated with this hormone for growth promotion purposes. Therefore, whether the concentrations of hormone residues in meat and meat products could be higher as a result of misuse or abuse did not have to be addressed. The Panel does not deem it necessary to move this section to another part of its findings.

6.155 Having regard to the point made by the European Communities that misuse and abuse in the administration of hormones is an aspect of risk assessment within the meaning of Article 5.1 to 5.3, the Panel reflected further on whether this issue related at all to the question of insufficiency of relevant scientific evidence under Article 5.7. In the view of the Panel, the question of whether JECFA properly took into account misuse and abuse in its risk assessments is irrelevant to the question whether the European Communities can take this matter into account in its own risk assessment, since it has full discretion to do so pursuant Article 5.2 and to the Appellate Body finding in *EC – Hormones*. In that context, whether evidence exists of misuse or abuse in the administration of hormones is not as such a scientific issue likely to make a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement* impossible.

6.156 For these reasons, the Panel decided to delete the section regarding misuse or abuse in the administration of hormones from its final report and modified paragraph 7.578.

6.157 The European Communities argues that the Panel's analysis on the issue of carcinogenicity of progesterone in Section VII.C.3(f)(vii) is flawed. However, the European Communities does not explain specifically in what respect it is flawed. The Panel therefore did not modify its reasoning.

6.158 The European Communities argues that the Panel's analysis on the issue of carcinogenicity and genotoxicity of testosterone in Section VII.C.3(f)(viii) is clearly incorrect and flawed. The European Communities refers to a statement by Dr. Tritscher allegedly admitting that JECFA found that there was scientific uncertainty about genotoxicity of testosterone.[303] The Panel consulted the transcript and noted that Dr. Tritcher discussed the genotoxicity of oestradiol, not that of testosterone. She did say that "all information is being looked at, in particular with compounds that have a genotoxic potential", but she did not mention that progesterone had a genotoxic potential.

6.159 The European Communities argues that the approach and analysis of the Panel on the issue of metabolism and carcinogenicity of trenbolone acetate in Section VII.C.3(f)(ix) is flawed, *inter alia*, because JECFA's assessment defended by Dr. Boobis and Dr. Boisseau dates back to 1988 and is clearly outdated. The Panel has already discussed this argument and considers that a risk assessment does not become invalid merely because it is "old". The Panel believes that, in order to demonstrate that a risk assessment is "outdated", a party must provide studies showing that the data on which the risk assessment is based are no longer valid.

6.160 The European Communities argues that the reasoning of the Panel regarding carcinogenicity of zeranol is flawed, *inter alia*, because if the extrapolation to meat consumption mentioned by Dr. Guttenplan was necessary, as the Panel seems to require in paragraph 7.783, this would have amounted to a complete risk assessment in the sense of Article 5.1 of the *SPS Agreement*. The

[303] Statement of Dr. Tritcher, Annex G, para. 463.

European Communities argues that this is not the relevant standard in the context of Article 5.7. We agree with the European Communities that being able to perform a risk assessment compatible with Article 5.1 is not the standard applicable in the context of Article 5.7 and we do not consider that we applied any such standard in this case. Indeed, the reason why the Panel paraphrased Dr. Guttenplan's statement was not to say that the European Communities could demonstrate that relevant scientific evidence was insufficient only if it were able to extrapolate some genotoxic effect of zeranol to meat consumption. The point that the Panel wanted to make was that the extrapolation of the study commented by Dr. Guttenplan would have entailed, according to Dr. Guttenplan, a "myriad of uncertainties". As a result, this study could hardly serve as a basis to put in question existing knowledge. We clarified this in paragraph 7.783.

6.161 As regards the alleged application of a similar standard in paragraphs 7.787-7.788, the Panel recalls that what has to be demonstrated for Article 5.7 to apply is that no risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement* can be performed. Our reference to Dr. Guttenplan means that we consider, as mentioned in paragraph 7.615, that not just any form of scientific uncertainty can justify a recourse to Article 5.7. As previously noted, we consider that when scientific evidence has been sufficient, it may only be considered as insufficient if a critical mass of scientific information and evidence exists, in terms of quantity and quality, to put into question existing knowledge and evidence. We therefore did not consider it necessary to modify our reasoning.

6.162 In paragraph 7.798, the European Communities expresses its disagreement with the Panel's approach consisting of applying a presumption of conformity with the *SPS Agreement* to JECFA's risk assessment on melengestrol acetate (MGA), even though that risk assessment has not yet been endorsed by Codex. The Panel has explained in paragraph 7.799 why some degree of relevance should be given to JECFA's work, even though it is not formally a "standard, guideline or recommendation" within the meaning of Article 3.2 of the *SPS Agreement*. The Panel also notes that the European Communities does not specify in which respect the Panel's analysis of the issue of the residue data used by JECFA on carcinogenicity is flawed, except for suggesting that the residue data is "outdated", a question already addressed by the Panel in paragraphs 7.800-7.803.

6.163 Finally, the European Communities requests the Panel to clarify the meaning and extent of its conclusion in paragraph 7.823. This paragraph simply states that, because relevant scientific evidence is not insufficient, the European Communities cannot invoke Article 5.7. The corollary is that the European Communities should be able to complete a risk assessment under Article 5.1. The European Communities argues that the Panel should clarify further how the risk assessment could be completed in the presence of the gaps identified in the EC Opinions with respect to oestradiol-17β. The gaps identified in the EC Opinions for oestradiol-17β are:

(a) that the European Communities has not evaluated specifically the possibility of the adverse effects related to the association between excess hormones and neurobiological, developmental, reproductive and immunological effects, as well as immunotoxicity, genotoxicity and carcinogenicity coming into being, originating or resulting from the consumption of meat or meat products which contain veterinary residues of oestradiol-17β as a result of the cattle being treated with this hormone for growth promotion purposes;

(b) The scientific evidence referred to in the Opinions does not support the European Communities' conclusions on genotoxicity, or the conclusion that the presence of residues of oestradiol-17β in meat and meat products as a result of cattle being treated with the hormone for growth promotion purposes leads to increased cancer risk. The scientific evidence does not support the EC conclusions on the adverse

> immunological and developmental effects of consuming meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes.

6.164 Thus, the problems identified by the Panel are not related to the fact that a risk assessment cannot be performed, but rather that the European Communities did not conduct a risk assessment pursuant to Article 5.1 and Annex A(4) and that the scientific evidence did not support the conclusions which the European Communities reached. The European Communities' comment apparently underlines an approach to risk assessment that seems to consist of identifying a risk from a particular substance and if there is any possibility, no matter how remote, of that risk occurring because of that substance, deciding that there is no need to further study whether the risk could arise from the levels of that substance found in food, beverages, or feedstuffs. As discussed in paragraph 6.107 above, the purpose of a risk assessment under Article 5.1 and Annex A(4) is not to provide guarantees that risks will be below a particular appropriate level of protection or even zero, but to objectively determine the possibility for the risk to arise from the presence of the substance under review in food, beverages, or feedstuffs. The Panel therefore, does not believe that the European Communities' approach to risk assessment, whereby the desired level of protection informs the risk assessment rather than the risk assessment providing objective data to be utilized by a government in determining how to achieve its appropriate level of protection, is consistent with the object and purpose of Article 5 of the *SPS Agreement.*

(b) Comments by Canada

6.165 Canada points out that the first sentence of paragraph 7.509 states that "the European Communities has assessed the general risk of the identified potential adverse health effects ..." (emphasis added). Canada requests, given the specific definition of risk assessment in the *SPS Agreement*, that the Panel replace the phrase "has assessed the general risk" with the phrase "has identified a hazard in relation to".[304] The European Communities, in its comments of 19 October 2007[305], argues that the Appellate Body has already found, in *EC – Hormones*, that the EC risk assessment at that time had indeed shown the "existence of a general risk of cancer".[306]

6.166 Considering that it was necessary to ensure clarity, the Panel decided to modify paragraph 7.509. However, the Panel will not use the term "has identified a hazard in relation to" as this too has very specific meanings as set forth in the Codex Procedural Manual and cited in paragraph 7.437. Instead, it will modify paragraph 7.509 to read:

> "All of the statements of the experts, and indeed statements from the Opinions, indicate that the European Communities has evaluated the potential for the identified adverse effects to be associated with oestrogens in general, but has not provided analysis of the potential for these effects to arise from consumption of meat and meat products which contain residues of oestradiol-17β as a result of the cattle they are derived from being treated with the hormone for growth promotion purposes."

6.167 The Panel also considers this correction to be in line with the finding of the Appellate Body in paragraph 200 of its report on *EC – Hormones* referred to above by the European Communities.

6.168 Canada also requests that we replace, in paragraph 7.842(a), the phrase "to the extent that" by the term "because". The Panel does not deem it appropriate to accept Canada's suggestion since the reason for the violation of Article 22.8 in this case is only one of the reasons that can lead to a violation of that Article.

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[304] Canada's comments on interim report, p. 4.
[305] Para. 23.
[306] Appellate Body Report on *EC – Hormones*, para. 200.

VII. FINDINGS

A. PROCEDURAL ISSUES

1. Opening of the Panel meetings with the parties and experts for public observation

(a) Introduction

7.1 On 13 June 2005, at the first organizational meeting of the Panel, the parties jointly requested that the Panel's substantive meetings with parties be open for public observation. Through written questions, the Panel requested the parties to specify the legal basis in the DSU for such a request. Parties replied on 20 June 2005. On 30 June 2005, the Panel posed additional questions to the parties on the logistical implications of a hearing that was open to the public. The parties replied on 7 July 2005. The Panel held a second organizational meeting with the parties to discuss this issue on 8 July 2005.[307]

(b) Summary of the main arguments of the parties[308]

7.2 With reference to the Panel's question whether panels are permitted to open hearings to public observation under Articles 12 (including Appendix 3), 14.1 and 17.10 of the DSU, the **European Communities** argues that a panel may adopt working procedures that foresee open hearings, as Article 12.1 of the DSU provides that panels may depart from the working procedures in Appendix 3 after consulting the parties to the dispute.

7.3 The European Communities also argues that this conclusion is not affected by Article 14.1 of the DSU on confidentiality of panel deliberations. The term "deliberations" does not cover the meetings with the parties, for which a different terminology is used in Appendix 3 of the DSU.

7.4 The European Communities considers that in the present case where all the parties have agreed to open hearings, the Panel should accommodate the parties' request. Article 18.2 of the DSU also supports the position that parties are entitled to "waive" the confidentiality of their positions.

7.5 Regarding the legal implications of open hearings on covered persons under the Rules of Conduct, the European Communities considers that no legal issues arise under the Rules of Conduct. In the European Communities view, the Rules of Conduct are and remain fully binding on all covered persons in this dispute, even if the hearings are opened to the public. The Panel's deliberations will in any event not be affected by the opening and remain confidential, as required by Article 14.1 of the DSU.

7.6 With respect to the systemic and political impact of opening hearings, the European Communities is of the view that there are no implications for WTO Members who are not parties to this dispute, or on the intergovernmental character of the WTO, nor would it impair the chances to reach a mutually agreed solution, as preferred by the DSU (Article 3.7). Also, there are no implications for third parties because the parties have jointly requested that the public be excluded from the third parties' session during the presentation by a third party, unless that third party agreed to make its presentation open for observation by the public.

[307] The parties agreed to hold joint panel meetings in this case and that against the United States (WT/DS320) and to harmonize the Panels' timetables.

[308] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report.

7.7 Regarding the procedures that may be adopted to protect confidential information in an open hearing, the European Communities indicates that it does not expect that confidential information will be submitted in this dispute. The European Communities does not consider that there is any issue of confidentiality in relation to information submitted by other Members or non-Members (under Article 13 of the DSU), unless the confidentiality requirement of the last sentence of Article 13.1 of the DSU applies, in which case the corresponding portion of any meeting where this information is discussed could be closed.

7.8 With respect to the third-party session, the European Communities considers that each third party should decide whether to open the part of the third-party session dealing with that third-party's statement.

7.9 **Canada** argues that the DSU allows for open hearings of WTO panels. Article 14.1 of the DSU states that panel "deliberations" shall be confidential. The reference to "deliberations" indicates that this paragraph applies to the internal deliberations of panels, not to the panels' meetings with the parties. Furthermore, paragraph 2 of the Working Procedures in Appendix 3 of the DSU, which refers to closed panel meetings, is subject to DSU Article 12.1, which specifically allows a panel to deviate from the Working Procedures in Appendix 3 after consulting parties to the dispute. In cases such as this one, where all parties to the dispute have agreed to open hearings, Canada is of the view that the Panel should accommodate such a request. This position is consistent with the right of all parties to waive confidentiality as expressed in Article 18.2 of the DSU, which states that a party is not precluded from disclosing statements of its own positions to the public. In the present case, it is clear that all parties have agreed beforehand to waive their right to confidentiality during the panel hearings.

7.10 Canada argues that the relevant provision in the Rules of Conduct is paragraph VII.1, which provides: "[e]ach covered person shall at all times maintain the confidentiality of dispute settlement deliberations and proceedings together with any information identified by a party as confidential. No covered person shall at any time use any information acquired during such deliberations and proceedings to gain personal advantage or advantage for others."

7.11 This provision, in Canada's view, requires confidentiality on the part of members of a panel of deliberations and proceedings. However, in accordance with paragraph II:1 of the Rules of Conduct, which expressly states that these Rules do not modify the rules and procedures under the DSU, this provision is subject to a decision of the Panel to hold public hearings pursuant to Article 12.1 of the DSU. Therefore, Canada considers that the obligation of covered persons to maintain the confidentiality of a panel proceedings continues to apply but is modified to the extent that the Panel has decided to hold public hearings.

7.12 Canada considers that opening the panel meetings to the public can only contribute to the legitimacy, and perception of legitimacy, of the dispute settlement process. The desire of the disputing parties to hold open hearings in this case does not have any broader systemic or political implications – it merely serves the interests of the disputing parties in this case consistent with the institutional framework of the WTO and with Article 12.1 of the DSU.

7.13 Canada submits that Article 12.1 of the DSU requires that panels' decisions on their working procedures be taken in view of consultation with parties. This provision does not require consultation with third parties. However, Canada recognizes that third parties may have requested third party status with the expectation of participating in closed proceedings. Therefore, Canada suggests that after the Panel decides to hold public hearings it should consult with third parties to (a) identify any concerns of third parties regarding their participation in the proceedings, and (b) explore possible steps to accommodate such concerns. Such accommodation measures may include turning off cameras during the delivery of oral statements of third parties that do not wish to deliver such an oral

statement in a public hearing. Canada does not see a need for the Panel to consult with the Chairs of the DSB, of the General Council or of the DSB Special Sessions, or with the Director General.

7.14 Canada believe that a provision should be added to the Working Procedures that would provide a mechanism to protect business-confidential information that may become the subject of discussion during the public hearings. Canada recommends a procedure under which a party may request the Panel to suspend the public nature of the hearing for as long as such business-confidential information was being discussed.

7.15 As to the third parties, Canada submits that they will have to follow the provisions in the Working Procedures adopted by the Panel pursuant to DSU Article 12. Thus it is open to the Panel to decide that the oral statements by third parties will take place in public meeting. However, it is also within the Panel's discretion to leave it to the choice of individual third parties whether they wish to make their oral statements in a private or public session. Canada prefers giving third parties such a choice. Canada recommends the adoption of a practical procedural mechanism to suspend the public nature of the hearing as necessary.

7.16 Finally, Canada considers that the treatment of written materials presented by other WTO Members or by non-Members falls outside the scope of issues raised by the possible public nature of the hearing. None of the parties has proposed a modification to the Working Procedures that would expand the categories of participants in the hearing. Nevertheless, Canada recognizes that the written evidence provided by other WTO Members or non-Members may have been provided in confidence. To the extent that such confidential information is discussed during the hearings, there will be need to add to the Working Procedures a provision that would permit the Panel to interrupt the public nature of the hearing before a discussion of such confidential written materials takes place. In Canada's view, such a procedure should be similar to that outlined above in respect of business-confidential information.

(c) Summary of the arguments of the third parties[309]

7.17 **Australia** contends that when parties agree not to follow the Working Procedures in Appendix 3, or parts thereof, it would be difficult for the Panel to justify a decision that goes against the wishes of the parties. In Australia's view, to do so would undermine a basic principle of dispute settlement whereby parties consult with each other and with the Panel and seek mutual agreement on the conduct of disputes, according to Article 12.1 of the DSU.[310]

7.18 While not objecting to the opening of the Panel's hearing for public observation, Australia is however concerned about the modalities of organizing the meetings, equity of access and logistic issues and believes that the opening of the Panel's meetings to the public should be subject to the provisions that allow for protection of confidential information.[311]

7.19 **Brazil** questions the specific grounds and the DSU provisions on which the Panel based its decision to accept the parties' request to open the Panel meetings for public observation. According to Brazil, transparency constitutes an important element in the debate carried out by Members in DSB meetings, which will largely benefit from any further clarification by the Panel as to the legal reasons which motivated its decision to open the meetings to the public.[312]

[309] A more detailed account of the third parties' arguments can be found in Section V of the descriptive part of this Report.
[310] Replies by Australia to Panel questions concerning open hearings, question 1.
[311] Replies by Australia to Panel questions concerning open hearings, question 2.
[312] Oral statement of Brazil, para. 2.

7.20 Brazil argues that a decision on whether or not to open panels' proceedings to the public relies solely on the WTO membership, in particular the DSU review process which is the appropriate *locus* to deal with issues regarding the dispute settlement mechanism. According to Brazil, if panels were to decide on this issue, they would go beyond their mandate, playing a role that is exclusive to the WTO membership.[313]

7.21 Brazil also contends that opening the meetings to the public would represent a reinterpretation of Article 14 of the DSU, signalling that there are cases to which confidentiality is not applied, such as Panel and Appellate Body meetings.[314]

7.22 **China** prefers the Panel to meet the third parties in closed session. It argues that based on Article 18.2 of the DSU, panels do not have the right unilaterally to disclose the third-party submissions and oral presentations.[315]

7.23 **India** submits that the issue of external transparency is being discussed in the ongoing negotiations in the Special Session of the DSB. Until there is a consensus on the opening of panel meetings to public observation and the modalities therefor, India believes that the Panel proceedings have to be in closed session[316], and its deliberations have to remain confidential[317] as provided in the DSU.[318]

7.24 India contends that the possibility of a panel to decide to deviate from the Working Procedures in Appendix 3 has been provided with the view of having panel procedures with sufficient flexibility so as to ensure high-quality panel reports.[319] In India's view, although panels are given some discretion in establishing their own working procedures, they do not have the discretion to modify the substantive provisions of the DSU, such as confidentiality requirements.[320]

7.25 India argues that Article VII of the Rules of Conduct[321] requires each "covered person" to maintain the confidentiality of dispute settlement deliberations and proceedings at all times. India questions how the Panel is going to ensure that these requirements are met after opening the proceedings to the public for observation.[322]

7.26 India submits that the decision of the Panel to open its proceedings to the public necessarily involves some issues on which consultation and decisions with WTO Members, and not just the parties and third parties, would have been necessary. For example, India questions how the Panel, at its own level, addressed issues relating to the implications on the functioning of the WTO Secretariat, budgetary implications and implications relating to the use of the official languages of the WTO, for which rules and practices have been established by other bodies of the WTO. India also questions how the Panel could take a view on the additional costs arising out of the opening up of the proceedings to public without the Budget Committee having considered the matter.[323]

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[313] Replies by Brazil to Panel questions concerning open hearings, question 1.
[314] Replies by Brazil to Panel questions concerning open hearings, question 1.
[315] Replies by China to Panel questions concerning open hearings, questions 1 and 2.
[316] Paragraph 2 of the working procedures in Appendix 3 of the DSU
[317] Paragraph 3 of the working procedures in Appendix 3 of the DSU
[318] Replies by India to Panel questions concerning open hearings, question 1.
[319] Article 12.2 of the DSU.
[320] Oral statement of India, para. 6.
[321] Rules of Conduct for the Understanding on Rules and Procedures Governing the Settlement of Disputes, adopted by the DSB on 3 December 1996 (WT/DSB/RC/1).
[322] Oral statement of India, para. 7.
[323] Oral statement of India, para. 8.

7.27 According to India, the WTO is a Member-driven organization and it is solely for the WTO Members to decide whether or not to change the WTO rules and open up panel proceedings to the public; a Panel cannot take upon itself that function, even at the request of parties to the dispute.[324]

7.28 India posits that the meeting of the Panel with the third parties should be in closed session as required under paragraph 2 of the Working Procedures contained in Appendix 3 of the DSU. [325]

7.29 **Mexico** disagrees with the opening of the Panel meetings to the public on the grounds that panel meetings constitute panel "deliberations" and as such should be confidential, as per Article 14.1 of the DSU. Mexico also argues that transparency is a sensitive issue that is currently under discussion in the negotiations to amend the DSU. Mexico argues that the DSU rules require that the meetings be confidential and, therefore, the decision of the two parties should only prevail to the extent that it does not affect the right of other Members including third parties.[326]

7.30 Mexico emphasizes that public hearings are a cross-cutting issue that should be addressed in general by the WTO, and should not be imposed by a panel at the request of two Members. Mexico regrets that the decision will set a precedent that may affect the outcome of the negotiations and will in all likelihood end up complicating the preparation of working procedures of future panels.[327] Mexico suggests that the third-party session follow the established WTO practice of being held in closed session.[328]

7.31 According to **New Zealand**, there are no legal constraints that would prevent the Panel from opening its hearings to the public. New Zealand quotes Article 12.1 of the DSU which allows panels to follow the working procedures in the DSU unless the panel decides otherwise after consulting the parties. New Zealand argues that while Appendix 3 provides for closed session hearings, the working procedures can be amended with the consent of the Panel and the parties. New Zealand further notes that the reference in Article 14.1 of the DSU to panel deliberations being confidential refers to the internal deliberations of the panel, not the hearings with the parties. New Zealand submits that this is in line with the practice of other international tribunals which have open hearings but whose deliberations are nonetheless confidential. According to New Zealand, Article 18.2 of the DSU allows parties to waive confidentiality. New Zealand did not object to its third-party hearings being public.[329]

7.32 **Norway** considers that Article 12.1 of the DSU gives the Panel the discretion to follow other working procedures than the ones provided in Appendix 3 after consulting the parties. It sees no legal constraints in granting the parties request to open the hearings to the public. Norway also agrees to having the third party session of the hearing open to the public.[330]

7.33 The **Separate Customs Territory of Taiwan, Penghu, Kinmen and Matsu** (Chinese Taipei) argues that, in accordance with the procedures and customary practices developed over more than half a century under GATT, which are reflected in Articles 14.1, 18.2 and Appendix 3 of the DSU, panel proceedings are to be kept confidential. It argues that only Members by consensus can

[324] Oral statement of India, para. 9.
[325] Replies by India to Panel questions concerning open hearings, question 2.
[326] Oral statement of Mexico, para. 2; Mexico's replies to Panel questions following the first substantive meeting of the Panel, paras. 9 and 3.
[327] Oral statement of Mexico, para. 3.
[328] Replies by Mexico to Panel questions concerning open hearings, question 2.
[329] Replies by New Zealand to Panel questions concerning open hearings, questions 1 and 2.
[330] Replies by Norway to Panel questions concerning open hearings, questions 1 and 2.

change the rules of confidentiality. According to Chinese Taipei, a panel, even with the consent of the parties does not have the legal authority to open the proceedings to the public.[331]

7.34 Chinese Taipei refers to Article VII of the Rules of Conduct which requires that each covered person shall at all times maintain the confidentiality of the dispute settlement deliberations and proceedings. According to it, the only exception to this confidentiality obligation is Article 18.2 of the DSU. Chinese Taipei is therefore of the opinion that this exception does not extend to the possibility of allowing parties to decide whether to open panel meetings to the public.[332]

7.35 According to Chinese Taipei, "panel deliberations" implies more than one form of deliberation, thus including not only internal consideration among panelists, but also the entire process of the panel's consideration of the dispute.[333]

7.36 Chinese Taipei argues that the flexibility arising from Article 12.1 of the DSU to change working procedures in Appendix 3 cannot be extended to cover provisions in the working procedures that directly elaborate on the obligations of the DSU. It further argues that if the drafters had contemplated that the confidentiality requirement could be changed, they would have said so, just like in Article 18.2 of the DSU. In the absence of such language, only an amendment to the DSU by the Members through negotiations can change the requirement of confidential deliberations.[334]

7.37 Chinese Taipei is of the opinion that the third-party sessions should be held in closed session.[335]

(d) Decision of the Panel

7.38 On 1 August 2005, the Panel decided to accept the parties' joint request to open the Panel hearings for public observation. The Panel also decided that the meetings at which the parties are invited to appear, as referred to in paragraph 2 of Appendix 3 to the DSU, would be open for observation by the public through a closed-circuit broadcast, keeping in mind the Panel's obligation to ensure that its Working Procedures are objective, impartial and non-discriminatory, and after careful consideration of the existing provisions of the DSU and its Appendix 3. In addition, since not all third parties had agreed that their session with the Panel be open for observation by the public, the Panel decided that that session would remain closed. As provided in paragraph 3 of the Panel's Working Procedures[336], the parties retain the right to request at any time, including during panel meetings at which they are invited to appear, that their specific statements not be broadcast so as to remain confidential. The Panel also reserved its right to decide on its own to suspend broadcasting at any time, including during such meetings.[337] The Panel sent its revised Working Procedures and timetable to the parties and third parties on 1 August 2005.

7.39 The Chairman of the Panel also sent letters to the Chairman of the DSB[338] and the Director-General of the WTO[339], informing them of the Panel decision on this matter and requesting the

[331] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, paras. 1 and 2.
[332] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, para. 4 and 5.
[333] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, para. 3.
[334] Replies by Chinese Taipei to Panel questions concerning open hearings, question 1, paras. 6 and 7.
[335] Replies by Chinese Taipei to Panel questions concerning open hearings, question 2, para. 12.
[336] The Panel's working procedures are contained in Annex A-2 to this report.
[337] The letter of the Panel to the Parties of 1 August 2005 is reproduced in Annex A-1 to this Report.
[338] See WT/DS321/8, 2 August 2005.
[339] Letter of the Chairman of the Panel to the Director-General of the WTO of 2 August 2005. The letter reads as follows:

> "On behalf of the Panels in the two cases referred to above, I would like to request your assistance concerning the implementation of a procedural decision taken by the Panels.

assistance of the WTO Secretariat in making appropriate logistical arrangements for the open hearings.

7.40 After the Panel decided to consult scientific experts[340], the opinion of the parties was sought on whether they wished that any meeting with the parties and the scientific experts also be open for public observation. The parties replied affirmatively.

7.41 Since this was the first time in GATT/WTO history that a panel has held hearings open for public observation, the Panel deems it appropriate to elaborate further on the reasons why it agreed to open its substantive meetings for public observation.

7.42 The Panel first wishes to recall that it acted at the joint request of the parties. Some third parties, however, objected to the holding of a hearing that would be observable by the public. As a result, the hearing with third parties was not opened to public observation.

7.43 The Panel considers that the DSU does not expressly contemplate the possibility for meetings of panels to be open for public observation. On the contrary, Paragraph 2 of Appendix 3 to the DSU provides that "the panel shall meet in closed session" and that "The parties to the dispute, and interested parties, shall be present at the meeting only when invited by the panel to appear before it." The Panel understands this to mean that it shall always meet *in camera*, whether or not the parties and/or interested parties have been invited to appear before it. No reference is made in that provision to other Members or to the general public.

7.44 However, Article 12.1 of the DSU provides that "[p]anels shall follow the Working Procedures in Appendix 3 unless the panel decides otherwise after consulting the parties to the dispute." In other words, the Panel has the possibility to depart from any provision of Appendix 3, its only obligation being to consult the parties to the dispute first.

> Following a common request made by the parties on 13 June 2005, we have decided that the panel meetings to which the parties are invited to appear will be open for observation by the public through a closed-circuit TV broadcast. We informed the parties of our decision on 1 August 2005. The session with the third parties will remain closed as not all the third parties have agreed to have it open for observation by the public. The third parties were advised of our decision on 1 August 2005. Finally, the Chairman of the DSB has also been advised of our decision, with a request that he informs the entire DSB membership of the possibility to observe the hearings.
>
> The Panels appreciate the assistance of the Secretariat on these cases to date and would like to request continued Secretariat assistance with respect to the logistical arrangements needed to implement our decision. In this regard, we would like to ensure transparency and non-discriminatory access by all, in particular by all WTO Members, to the closed-circuit TV broadcast. For that purpose, we would request the Secretariat to guarantee that each WTO Member delegation has <u>at least</u> two seats available in the room where the closed-circuit broadcast will be shown. We would also ask the Secretariat through its website to make all Members and the public aware that they are allowed to attend the closed-circuit broadcast and to provide details on pre-registration and seating arrangements.
>
> We have scheduled the first substantive meeting of the Panels with the parties for 12-15 September 2005 and understand that this meeting could take place in Room W with a closed-circuit TV broadcast of the meeting in the General Council Room.
>
> I would greatly appreciate your assistance in ensuring that the logistical arrangements to which I have referred in this letter can be finalized by the Secretariat."

[340] See Section VII.A.2 below.

7.45 This discretion, however, applies only to the provisions of the Working Procedures in Appendix 3, not to any other provision of the DSU. The Panel thus is of the view that Article 12.1 entitles it to proceed with any adaptation of the working procedures contained in Appendix 3, as long as such an adaptation is not expressly prohibited by any provision of the DSU. Therefore, we need to examine whether there is any DSU provision that would explicitly prohibit the opening of panel meetings to public observation.

7.46 The Panel notes in this respect the confidentiality requirements contained in Articles 14.1, 18.2 and Appendix 3, paragraph 3 to the DSU. It also recalls the obligations of its members pursuant to the Rules of Conduct for the Understanding on Rules and Procedures Governing the Settlement of Disputes.[341]

7.47 Regarding the requirement in Article 14.1 of the DSU that "[p]anel deliberations shall be confidential", the Panel first notes that one of the ordinary meanings of the word "deliberations" is "careful consideration, weighing up with a view to decision". The term "deliberations" also applies to "[c]onsideration and discussion of a question by a legislative assembly, a committee, etc.; debate".[342] However, the Panel is not of the view that a panel hearing is similar to a consideration by a legislative body or a committee. Even though exchanges of points of view take place in both instances, the nature of the exchange of arguments by parties to a dispute before an adjudicating body remains different from that of an assembly or a committee. This suggests that the term "deliberation" was not intended to cover the exchange of arguments between the parties, but rather the internal discussion of the Panel with a view to reach its conclusions. We note that our interpretation of the term "deliberation" conforms to the use of that term in the statutes of other international judicial bodies.[343] It is also confirmed by the context of Article 14.1. Article 14 deals with confidentiality in the work of panels *stricto sensu* (deliberations, drafting of the panel report, opinions of panelists), whereas the provisions dealing with the conduct of the proceedings with the parties are contained in Article 12. The Panel therefore concludes that Article 14.1 of the DSU does not apply to panel hearings and that opening the Panel's substantive meetings with the parties to public observation does not breach that provision.

7.48 Regarding the requirement contained in Article 18.2 of the DSU that "[w]ritten submissions to the panel ... shall be treated as confidential", we note that, by opening its hearings to public observation, the Panel did not disclose to the public the content of the parties' written submissions. By making statements to which the public could listen, the parties themselves exercised their right under Article 18.2 to "disclos[e] statements of [their] own positions to the public". The Panel is mindful that, by asking questions or seeking clarifications during the hearings with respect to written submissions of the parties, it may have itself "disclosed" the content of such submissions. However, the Panel notes that at all times the parties retained the right to request that specific statements of theirs not be broadcasted so as to remain confidential and that, in this case, the parties had made their

[341] WT/DSB/RC/1, 11 December 1996.

[342] *The New Shorter Oxford English Dictionary* (4th ed., 1993), p. 624.

[343] Article 46 of the Statute of International Court of Justice provides that "[t]he hearing in Court shall be public, unless the Court decides otherwise, or unless the parties demand that the public be not admitted". Article 54.3 of the Statute provides that "[t]he deliberations of the Court shall take place in private and remain secret ...". Article 26 of the Statute of the International Tribunal for the Law of the Sea provides that "[t]he hearing shall be public, unless the Tribunal decides otherwise, or unless the parties demand that the public be not admitted". Article 42 of the Rules of the Tribunal provides that" [t]he deliberations of the Tribunal shall take place in private and remain secret ...". Article 20 of the Statute of the International Criminal Tribunal for Former Yugoslavia provides that "[t]he hearing in Court shall be public, unless the Trial Chamber decides to close the proceedings in accordance with its rules of procedure and evidence". Rule 78 of its Rules of Procedure and Evidence provides: "[a]ll proceedings before a Trial Chamber, other than deliberations of the Chamber, shall be held in public, unless otherwise provided." Rule 29 provides that "[t]he deliberations of the Chambers shall take place in private and remain secret."

written submissions public. The Panel notes also that Article 18.2 provides that "Members shall treat as confidential information submitted by another Member to the Panel or the Appellate Body *which that Member has designated as confidential*."[344] We consider that this sentence clarifies the scope of the confidentiality requirement which applies to the Panel and to Members, and that panels have to keep confidential only the information that has been designated as confidential or which has otherwise not been disclosed to the public. Any other interpretation would imply a double standard, whereby panels would have to treat as confidential information which a WTO Member does not have to treat as confidential. The Panel also notes that, by requesting that the Panel hold hearings open to public observation, the parties to this dispute have implicitly accepted that their arguments be public, with the exception of those they would identify as confidential.

7.49 Finally, the Panel notes that Article VII of the Rules of Conduct for the Understanding on the Rules and Procedures Governing the Settlement of Disputes provides that "[e]ach covered person shall at all times maintain the confidentiality of dispute settlement deliberations and proceedings together with any information identified by a party as confidential." The Panel notes that such confidentiality obligation on the covered persons during the panel proceedings is applicable to the extent not inconsistent with the DSU provisions.[345] In this case, the parties waived their right to confidentiality and requested open hearings. As demonstrated above, the Panel accordingly adapted its working procedures by departing from Appendix 3 in a manner consistent with the DSU provisions. Therefore, the Rules of Conduct should not be construed in a manner that would restrict the rights of Members under the DSU. The Panel concludes that Article VII does not prevent the Panel from holding hearings open to observation by the public.

7.50 The Panel is mindful that the issue of transparency of panel and Appellate Body proceedings is currently under review as part of the negotiations on improvements and clarifications of the DSU. However, the Panel recalls that the dispute settlement system of the WTO serves to preserve the rights and obligations of Members under the covered agreements, which include the DSU, and to clarify the existing provisions of those agreements in accordance with customary rules of interpretation of public international law. The Panel considers that its role is not to address transparency in general terms, but to determine whether the DSU as it currently stands permits that, under the circumstances of this particular case, the Panel hearing be open to public observation. When called upon to decide on whether to open hearings to public observation, the Panel concluded that this was the case. However, this finding is limited to this particular case and is without prejudice to any approach to the issue of transparency that the Members may negotiate.

7.51 For the reasons set out in the previous paragraphs, the Panel considers that it is entitled, under the particular circumstances of this case and pursuant to Article 12.1 of the DSU, to open its hearings for public observation. This is why the Panel decided to accept the parties' request to open its meetings with the parties for public observation. The third-party session was, however, not open to public observation, due to the absence of consensus among the third parties on this matter.[346]

7.52 The first substantive hearing with the parties was held on 12, 13 and 15 September 2005. The hearing with third parties took place on 14 September 2005. The hearing with the scientific experts was held on 27-28 September 2006. The second substantive meeting with the parties was held on 2 and 3 October 2006.

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[344] Emphasis added.

[345] See Rules of Conduct for the Understanding on Rules and Procedures Governing the Settlement of Disputes (WT/DSB/RC/1), Article II.1:

> "These Rules shall in no way modify the rights and obligations of Members under the DSU nor the rules and procedures therein."

[346] See WT/DS321/8.

2. Panel's decisions relating to the consultation of individual scientific experts and international organizations

(a) Decision to consult scientific experts

7.53 During its first substantive meeting, the **Panel** requested the parties' views on whether there was a need to consult scientific experts should the Panel deem it necessary to examine the consistency of the EC implementing measure with the *SPS Agreement* as part of its review of this case.[347]

7.54 The **European Communities** replied that it did not believe that it was necessary for this Panel to look into these scientific issues to make findings and rulings pursuant to its terms of reference. However, the Panel did not have the expertise to decide on such issues itself, should the Panel decide to review the scientific issues at stake. In such a scenario, the consultation of scientific and technical experts would be absolutely necessary. However, the European Communities considered that this Panel could not consult the experts that were used in the original *EC – Hormones* case. New experts would have to be chosen.[348]

7.55 **Canada** argued that should the Panel deem it necessary to consider whether the EC revised measure complies with the *SPS Agreement*, the complexity of the issues in this case would require consultation with scientific experts. Were the Panel to so decide, those experts should be consulted as to (a) whether the Opinions and/or studies relied on by the European Communities constitute the necessary risk assessment identifying the risks to consumers that flow from the ingestion of meat from animals treated with oestradiol-17β; (b) whether there is sufficient scientific evidence regarding the other five hormonal growth promotants at issue to enable the European Communities to conduct a risk assessment; and (c) whether current scientific knowledge warrants the EC ongoing ban regarding the six hormonal growth promotants.

7.56 Should the Panel decide to consult experts, in Canada's view, those experts who advised the panel in the original *EC – Hormones* case should be among the candidates. However, Canada might wish to propose several other recognized experts as candidates.[349]

7.57 After having considered the parties' replies, the **Panel** noted that, from the parties' replies to its questions, it appeared that no party disagreed that, should the Panel proceed with an assessment of the measure taken by the European Communities to comply with the recommendations and rulings of the DSB in the *EC – Hormones* case, advice from technical or scientific experts would be necessary.

7.58 The Panel noted the views expressed by the European Communities regarding the nature of this case and the order in which its claims should be reviewed by the Panel, but it was of the opinion that, at that stage, it was in its interest, as well as in the interest of the parties, to be fully informed of all relevant aspects of the dispute. The Panel thus decided to initiate a process for consultation with experts in relation to the technical or scientific aspects of the compatibility of the EC implementing measure with the relevant provisions of the *SPS Agreement*, without prejudice to the positions held by any party in this respect and without prejudice to the conclusions that the Panel would ultimately reach on the claims raised by the European Communities. The Panel informed the parties accordingly in a letter dated 20 October 2005.[350]

7.59 The Panel does not deem it necessary to add to its reasoning on this issue except to recall that, as specified by the Appellate Body in *US – Shrimp*:

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[347] Question 74 of the Panel after the first substantive meeting.
[348] EC's reply to Panel questions after the first substantive meeting, question 74, Annex B-1.
[349] Canada's replies to Panel questions after the first substantive meeting, Annex B-2.
[350] Annex A-3 to this Report.

> "... the DSU accords to a panel established by the DSB, and engaged in a dispute settlement proceeding, ample and extensive authority to undertake and to control the process by which it informs itself ... of the relevant facts of the dispute ... That authority, and the breadth thereof, is indispensably necessary to enable a panel to discharge its duty imposed by Article 11 of the DSU to 'make an objective assessment of the matter before it, including an *objective assessment of the facts of the case*.' "[351]

7.60 In this particular case, as explained further in the subsequent sections of this report and in spite of the approach of the European Communities focusing on the breach of certain provisions of the DSU by the defending party, the Panel deemed it important to consult experts in order to "make an objective assessment of the matter before it, including an objective assessment of the facts of the case." In addition, Article 11.2 of the *SPS Agreement* "explicitly instructs"[352] panels to seek expert advice in disputes under the *SPS Agreement* involving scientific and technical issues:

> "In a dispute under this Agreement involving scientific or technical issues, a panel should seek advice from experts chosen by the panel in consultation with the parties to the dispute."[353]

7.61 The Panel is mindful that this case is not exactly a dispute "under [the SPS] Agreement" since its terms of reference do not refer to the *SPS Agreement*. We nonetheless consider that, since we may have to determine whether the European Communities has complied with its obligations under the *SPS Agreement* if we need to determine whether Article 22.8 of the DSU has been breached, this dispute is, at least indirectly, "under [the SPS] Agreement".

7.62 We therefore conclude that our decision to consult scientific experts is consistent with the requirements of the DSU and the *SPS Agreement*.

(b) EC request for a single expert review group

7.63 Once it decided to consult scientific experts, the **Panel** sought comments from the parties on the proposed Working Procedures for Consultation with Scientific and/or Technical Experts, the technical or scientific aspects on which the Panel should consult experts and on whether the meeting with the experts and parties should be open for observation by the public.

7.64 In a letter dated 3 November 2005, commenting on the draft working procedures for the consultation of experts, the **European Communities** requested that a single expert review group be called upon to assist the Panel, arguing that it was important that the Panel receive consistent advice on the issues and that it would reduce the risk of the Panel having to review and decide between competing scientific views among the experts.

7.65 **Canada** replied that should a single expert group be appointed, experts would be required to arrive at common answers to the questions put to them. This meant consensus of all experts would be required for each answer to questions. Such a process would have serious repercussions for the consultation process.

7.66 Canada also argued that past panels had followed the practice envisaged in the Panel's proposed Working Procedures for Consultation with Experts, i.e. that the selected experts each provide their own advice in answer to questions from the Panel and the parties. In Canada's view, it is important that the answers of the experts can be evaluated against the background of the areas of

[351] Appellate Body Report on *US – Shrimp*, para. 106 (emphasis original).
[352] See Appellate Body Report on *Japan – Agricultural Products II*, paras. 127-128.
[353] Article 11.2 of the *SPS Agreement*, emphasis added.

expertise that each expert will bring to the process. To enable such an evaluation, Canada requested the Panel not to follow the single expert group approach that the European Communities had proposed.[354]

7.67 The **European Communities** commented that its request was based on a desire to ensure the legitimacy of the Panel's findings by providing for a systematic, coherent and non-polarizing approach to complex scientific issues. Conversely, if experts acted as individuals, the Panel ran the risk of having to review and decide between competing scientific views amongst the Panel's experts as well as the experts advising the parties. This would normally be very difficult, if not impossible, to do in a way that would ensure transparency, excellence and credibility in this contested area of scientific research.

7.68 The European Communities also drew the Panel's attention to Article 13.2 and Appendix 4 of the DSU, Article 11.2 of the *SPS Agreement* and Article 14.2 and Annex 2 of the *TBT Agreement* which, most probably for the reasons just mentioned above, all refer to the possibility to establish *expert review groups*. The European Communities did not see any reason to deviate from this normal procedure which the drafters of the WTO Agreements clearly preferred.[355]

7.69 The **Panel** reached its final decision on the working procedures for consultations with scientific and/or technical experts on 25 November 2005.[356] Regarding the form the consultation of the experts should take, the Panel was not persuaded that the EC suggestion to consult an expert review group was the preferable option. Firstly, the fields of competence proposed by the parties were quite varied, rendering it difficult to find individual experts with competence in most or all of these fields to serve in an expert review group. The fact that no expert would have a comprehensive knowledge of all the relevant subjects made it even more important for the Panel to seek advice from the experts on an individual basis on their respective fields of expertise. Secondly, the Panel wished to hear any dissenting or minority views among the experts rather than receiving a consensus text from an expert review group. The Panel did not consider that the risk that experts may have diverging opinions would generate difficulties as serious as those alleged by the European Communities. The Panel rather saw the risk that an expert review group would only agree on a minimum common position, thus depriving the Panel of a full picture of the problems. It was also worth noting that so far, all WTO panels had preferred to consult scientific and/or technical experts on an individual basis.

7.70 The Panel does not deem it necessary to add to the reasons mentioned above, except to clarify that, in its view, none of the provisions cited by the European Communities sets a preference for expert review groups. On the contrary, the consultation of expert review groups is mentioned only as one option, both in Article 13.2 of the DSU and in Article 11.2 of the *SPS Agreement* and the terms of those provisions suggest that panels enjoy wide discretion in deciding to seek or not the assistance of an expert review group rather than that of individual experts. Indeed, Article 13.2 of the DSU provides that:

> "Panels may seek information from any relevant source and may consult experts to obtain their opinion on certain aspects of the matter. With respect to a factual issue concerning a scientific or other technical matter raised by a party to a dispute, a panel may request an advisory report in writing from an expert review group."[357]

[354] Canada's letter to the Panel of 8 November 2005.
[355] EC's letter to the Panel of 11 November 2005.
[356] Annex A-5 to this Report. The Panel also decided that the meeting with the experts would be open for observation by the public in the same manner as the meeting with the parties.
[357] Emphasis added.

7.71 Article 11.2, second sentence, of the *SPS Agreement* provides that:

> "To this end, the panel may, when it deems it appropriate, establish an advisory technical experts group, or consult the relevant international organizations, at the request of either party to the dispute or on its own initiative."[358]

7.72 We read these provisions as leaving a wide margin of discretion to the Panel. We find confirmation of this reading in the Appellate Body Report on *EC – Hormones*, where the Appellate Body recalled that:

> "Both Article 11.2 of the *SPS Agreement* and Article 13 of the DSU enable panels to seek information and advice as they deem appropriate in a particular case ...
>
> We find that in disputes involving scientific or technical issues, neither Article 11.2 of the *SPS Agreement*, nor Article 13 of the DSU prevents panels from consulting with individual experts. Rather, both the *SPS Agreement* and the DSU leave to the sound discretion of a panel the determination of whether the establishment of an expert review group is necessary or appropriate."[359]

7.73 We therefore conclude that our decision complies with the DSU, the *SPS Agreement* and the practice of the Appellate Body.

(c) Experts selection process

7.74 One single expert selection process was carried out for the two cases WT/DS320 and WT/DS321.[360]

7.75 After receiving input from the parties, the Panel, in its letter of 20 January 2006, identified the need for expert advice in seven fields, namely:

(a) risk analysis, in particular, the conduct of a risk assessment as it relates to food safety;

(b) animal science, including good veterinary practices in relation to the administration of the six hormones[361] to cattle through implants or other means;

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[358] Emphasis added. *A contrario*, Article 14.2 of the *TBT Agreement* cited by the European Communities expressly limits the choice of the panel to a technical expert group.

[359] Appellate Body Report on *EC – Hormones*, para. 147.

[360] In this section, the term "Panel" refers to the Panel in case WT/DS320 and the Panel in case WT/DS321. The same individuals served as panelists in the two cases.

[361] The six hormones can be defined as follows:

> *Oestradiol-17β*
>
> Oestradiol-17β is the most potent mammalian oestrogenic sex hormone, responsible for female characteristics. It is a member of a class of compounds called steroids. In females, it functions in the ovarian cycle and maintains uterine health; in males it inhibits the synthesis of testosterone. It is produced primarily by the ovaries and the placenta. In cattle, it is administered either alone or in combination with testosterone, progesterone and trenbolone by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter. (Replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel Question 1 to the experts. Annex D, paras. 1; 7-8; 17)

(c) toxicology, including genotoxicity[362], and carcinogenicity[363] risks arising from the six hormones in meat;

(d) inspection, sampling and testing methods, particularly in relation to residue analysis and characterization with respect to the six hormones;

Progesterone

Progesterone is the major mammalian progestational hormone, responsible for maintaining pregnancy. It is a steroid and is secreted primarily by the corpus luteum in the ovary of adult females and in the placenta. Progesterone is used as a contraceptive and to correct abnormalities in the menstrual cycle. In cattle, it is administered to steer, usually in combination with oestradiol-17β or oestradiol benzoate by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter. (Replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel Question 1 to the experts. Annex D, paras. 2; 9-10; 18)

Testosterone

Testosterone is a mammalian androgenic hormone, responsible for male characteristics. It is a steroid and is produced primarily in the testes of adult males. In cattle, testosterone is administered in combination with oestradiol -17β or oestradiol benzoate by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter. (Replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel Question 1 to the experts. Annex D, paras. 3; 11; 19)

Trenbolone acetate

Trenbolone acetate is a synthetic steroid with anabolic (growth-stimulating) properties several fold above that of testosterone. In cattle, it is administered alone or in combination with oestradiol-17β by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter. (Replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel Question 1 to the experts. Annex D, paras. 5; 12; 20)

Zeranol

Zeranol is an oestrogenic substance produced by certain fungal, or mold, species. It is a non-steroidal anabolic (growth-stimulating) agent and has been used for the management of menopausal and menstrual disorders. Zeranol is administered to cattle either alone, or in combination with trenbolone acetate by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter (replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel Question 1 to the experts. Annex D, paras. 6; 13-14; 21). Although zeranol occurs naturally, it is sometimes referred to as one of the synthetic hormones, together with trenbolone and melengestrol acetate.

Melengestrol acetate

Melengestrol acetate (MGA) is an orally active synthetic progestogen about 30 times as active as progesterone. It is fed to female cattle to improve body weight and feed conversion (replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel Question 1 to the experts. Annex D, paras. 4; 15-16; 22).

[362] Ability to cause damage to genetic material (DNA). Such damage may be mutagenic and/or carcinogenic (Replies of Dr. Boobis and Dr. Guttenplan to Panel Question 2 to the experts. Annex D, paras. 41 and 58. See also Transcript of the Panel meeting with the experts, Annex G, paras. 85-90).

[363] Process of induction of malignant neoplasms (cancer) by chemical, physical or biological agents (replies of Dr. Boobis and Dr. Guttenplan to Panel question 2 to the experts. Annex D, paras. 44 and 60).

(e) human endocrinology[364], including endogenous[365] production of hormones by humans, in particular prepubertal children;

(f) dietary intake studies and epidemiology[366] linked to meat consumption;

(g) physiology, in particular related to the possible effects of the six hormones when consumed in meat on the immune and nervous systems, and growth and reproduction.

7.76 As stipulated in the Working Procedures for Consultations with Scientific and/or Technical Experts adopted by the Panel on 25 November 2005 after consultation with the parties[367], the Panel sought information not only from selected experts but also from three relevant international entities, the Codex Alimentarius Commission (Codex)[368], the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[369], and the International Agency for Research on Cancer (IARC).[370] While the questions to experts focused on the seven areas identified, the questions to the above-mentioned entities focused on institutional and procedural issues as well as definitions relevant to the case.

7.77 Pursuant to the Working Procedures the Panel, on 29 November 2005, requested the Secretariats of the Codex Alimentarius Commission, JECFA and the IARC to recommend names of

[364] *Endocrinology:* "A subspecialty of internal medicine concerned with the metabolism, physiology, and disorders of the endocrine system." (Webster Online Dictionary) The *endocrine system* is defined by the same dictionary as "The system of glands that release their secretions (hormones) directly into the circulatory system. In addition to the endocrine glands, included are the chromaffin system and the neurosecretory systems."

[365] *Endogenous:* "Produced inside an organism or cell. The opposite is external (exogenous) production." (Webster's Online Dictionary)

[366] "A branch of medical science that deals with the incidence, distribution, and control of disease in a population; the sum of the factors controlling the presence or absence of a disease or pathogen" (Merriam-Webster Online Dictionary (http://www.m-w.com/dictionary/epidemiology)).

[367] Annex A-4, letter from the Panel to parties on 25 November 2005, Annex A-5, Working Procedures for Consultations with Scientific and/or Technical Experts.

[368] The Codex Alimentarius Commission was established by FAO and WHO, under the Joint FAO/WHO Food Standards Programme, to develop international food standards, guidelines and other recommendations such as codes of practice; its First Session met in 1963. The main purposes of this Programme are protecting health of the consumers, ensuring fair trade practices in food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations. The Codex Alimentarius Commission is one of the three international standard-setting organizations referenced in the *SPS Agreement* (reference: Codex Alimentarius website – www.codexalimentarius.net). Within the framework of the Codex Alimentarius Commission and its procedures, the responsibility for providing advice on risk management lies with the Commission and its subsidiary bodies while the responsibility for risk assessment lies primarily with the joint FAO/WHO expert bodies and consultations.

[369] The Joint FAO/WHO Expert Committee on Food Additives (JECFA), which has been meeting since 1956, is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). Its work includes the evaluation of food additives, contaminants, naturally occurring toxicants and residues of veterinary drugs in food. JECFA serves as an independent scientific committee which performs risk assessments and provides advice to FAO, WHO and the member countries of both organizations. The requests for scientific advice are in general channelled through the Codex Alimentarius Commission (Codex). Some countries use information from JECFA in the establishment of national food safety control programmes and Codex adopts standards based on evaluations by JECFA (reference: *Fact Sheet – What is JECFA? See* Annex 1 attached to Annex E-2).

[370] The International Agency for Research on Cancer (IARC), established in 1965, is part of the World Heath Organization. IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships (reference: IARC website – www.iarc.fr).

candidate experts in the relevant fields. The Panel contacted the 22 experts suggested by those international entities and requested that those interested and available to provide advice to the Panel submit their curriculum vitae, including publication lists, and disclose potential conflicts of interests. Eleven experts were interested and available. The Panel provided all the information received from the experts to the parties, requesting them to indicate any compelling reasons why particular experts should not be chosen to provide advice to the Panel in this dispute. The parties provided their comments on the proposed experts on 16 January 2006. Canada provided comments on one issue in the EC comments on 19 January 2006, i.e. the exclusion of experts who had participated in JECFA's risk assessment work. The European Communities responded to Canada's comments on 30 January 2006.

7.78 Because the parties' positions with respect to the candidate experts differed significantly, on 20 January 2006, the Panel requested the parties to suggest further names of candidate experts, in application of paragraph 6 of the Working Procedures.

7.79 On 31 January 2006, the Secretary to the Panel sent letters to 49 additional experts suggested by the parties. The Panel Secretary requested that experts interested and available to provide advice to the Panel submit their curriculum vitae including a list of publications and a disclosure of any potential conflicts of interests.

7.80 Of the 71 experts suggested by the international organizations and the parties to the two disputes, 40 experts indicated that they were available and 35 responded to the request for curriculum vitae and information regarding potential conflicts of interests.

7.81 The information provided by the experts was sent to the parties. The parties were once again given the opportunity to comment on each expert and to provide any compelling reasons why particular experts should not be chosen to provide advice to the Panel in these disputes.

7.82 The parties provided their comments on the second set of experts names on 22 February 2006. The European Communities replied to comments from the United States and Canada on certain experts proposed by the European Communities in an additional letter to the Panel of 27 February 2006. The United States and Canada commented on the EC letter of 27 February on 1 and 2 March respectively. One party or another submitted objections with regard to all but one of the experts by arguing either that an expert lacked sufficient expertise in the areas of the dispute identified as needing scientific or technical expertise, or was affiliated with the government of a party to this dispute; or was affiliated with JECFA; or had received funding from the pharmaceutical industry; or had been involved in the regulatory approval of any of the six hormones.

7.83 On 24 March 2006, the Panel informed the parties of the names of the experts that it had selected. The Panel wishes to recall that, in the selection process, it amply consulted the parties and selected the experts in accordance with procedures previously determined by the Panel in consultation with the parties.[371] The Panel excluded experts with close links with governmental authorities directly involved in policy-making regarding the six hormones and experts with close links to pharmaceutical companies or involved in public advocacy activities. The Panel chose not to exclude *a priori* experts who had participated in the preparation and drafting of JECFA's risk assessments because this would deprive the Panel and the parties of the benefit of the contribution of internationally recognized specialists[372] and because the Panel was of the opinion that experts familiar with the JECFA reports would be well-placed to assist the Panel in understanding the work of JECFA extensively referred to by the parties in their submissions, in particular by the European Communities. Moreover, the Panel,

[371] Appellate Body Report on *EC – Hormones*, para. 148.

[372] See Annex E-2, JECFA's replies to Panel question 14, regarding the selection process of experts involved in JECFA's work.

who was fully aware of the fields of competence of these experts, considered that they would be competent to answer questions with respect to risk assessment regarding the hormones at issue. The Panel also decided not to exclude *a priori* all experts who were current or past governmental employees unless a potential conflict of interests could reasonably be assumed from their official functions. In selecting the experts, the Panel also had in mind the need to choose experts with expertise to cover all the fields identified as at issue in the dispute.

7.84 The experts selected by the Panel were:

Dr. Jacques Boisseau, Former Director, French Agency for Veterinary Medicinal Products;

Dr. Alan R. Boobis, Director, Experimental Medicine & Toxicology Division of Medicine, Faculty of Medicine, Imperial College London (also Professor of Biochemical Pharmacology at Imperial College London);

Dr. Hubert De Brabander, Professor and Head of Faculty of Veterinary Medicine, Department of Veterinary Public Health & Food Safety, University of Ghent, Belgium;

Dr. Ronald L. Melnick, US National Institute of Environmental Health Sciences;

Dr. Wolfgang G. Sippell, Deputy Director, Department of Pediatrics, University of Kiel; Head of the Division of Pediatric Endocrinology & Diabetology, Children's Hospital, Christian-Albrechts-University of Kiel, Germany;

Dr. Kurt Straif, Scientist, Unit of Carcinogenic Identification and Evaluation, International Agency for Research on Cancer, Lyon, France.

7.85 On 28 March 2006, the European Communities requested that the Panel reconsider its choice of two of the experts, reiterating concerns already discussed above by the Panel and arguing that these experts had real or perceived conflicts of interests that should disqualify them from assisting the Panel. The Panel carefully considered the European Communities' request, including the information given regarding potential conflicts of interests. The Panel found in particular that the statement that one expert had made before the French Senate in 1996 had not been made in relation to hormones used for growth promotion purposes. Rather, it had been made with respect to hormones used for medical treatment purposes. The Panel also found that the links of another expert with two companies involved in research and counselling were not in the area of veterinary drugs or hormonal substances. The Panel concluded that the EC objections regarding those two experts were not justified. Therefore, on 31 March 2006, the Panel gave notice to the parties that it had found no reason to change its decision concerning the selection of experts.[373] In addition, having considered the information available about the various candidates, the Panel found that these two experts were the best choices among the very few individuals available with expertise in the area of risk assessment and would be able to provide the Panel with insight on international standards on the hormones at issue.[374]

7.86 On 12 April 2006, the Panel gave notice to the parties that Dr. Melnick and Dr. Straif were no longer available to assist the Panel and that the Panel had chosen to replace these experts with:

[373] Letter dated 31 March 2006 from the Panel to parties.

[374] The Panel wishes to highlight the challenges it encountered in selecting experts There was a limited number of specialists suggested and actually available in each of the fields on which the Panel needed assistance and almost always one or more of the parties objected to that specialist. For example, only six of the identified available experts were deemed to have extensive expertise in risk analysis. All of these experts were objected to by at least one party.

Dr. Vincent Cogliano, Head of Programme, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer, Lyon, France; and

Dr. Joseph Guttenplan, Professor, Department of Basic Science, New York University Dental Center; Research Associate Professor, Department of Environmental Medicine, New York University Medical Center.

7.87 In choosing experts to replace Dr. Melnick and Dr. Straif, the Panel was especially mindful of the need to replace these experts with others who could cover the same fields of expertise. Of the final six experts selected, three were amongst those originally suggested by the European Communities and three were suggested by the international organizations consulted by the Panel.

7.88 Canada, in a letter dated 20 April 2006, requested that the Panel amend its list of experts to include an expert with specific expertise with respect to good veterinary practices and their practical application in a North American context. In a letter dated 10 May 2006, the European Communities objected to the request for an animal science expert made by Canada, stating that all relevant questions could already be answered by the six experts.

7.89 In light of the experts' replies as to which questions they would not be in a position to answer, and in light of the parties' comments, the Panel decided that it would first consider the written replies from the experts to the questions and then would determine if it was necessary to seek advice from additional experts. The Panel decided not to amend the list of selected expert unless there was a real need in the future and communicated its decision to the parties in a letter dated 10 May 2006.

7.90 Because the Panel had requested Dr. De Brabander and Dr. Boisseau to answer the questions on good veterinary practices to the extent that they could, and because all questions were ultimately answered by at least one of the selected experts, the Panel did not find a need to consult additional experts.

7.91 In accordance with the Working Procedures for Consultations with Scientific and/or Technical Experts adopted by the Panel in consultation with the parties, the experts were requested to act in their individual capacities and not as representatives of any entity.

7.92 On 24 February 2006, the Panel sent to the parties the draft questions to scientific experts and international organizations for comments. The parties provided the Panel with their comments on 15 March 2006. After considering the parties' comments and after revising the draft questions as necessary, the Panel sent its 62 written questions to the individual scientific experts and its 26 written questions to the three international organizations (namely Codex, JECFA and IARC) on 13 April 2006, together with the parties' submissions and accompanying exhibits.

7.93 The Panel requested that the experts and the international entities provide their written replies to the scientific and technical questions by 12 June 2006.[375]

7.94 The Panel, after receiving replies from experts and Codex, JECFA, and IARC, forwarded these replies to the parties on 14 June for their comments. The parties provided their comments on these replies on 30 June 2006.[376] Afterwards, parties were given a further opportunity to comment on

[375] A compilation of the written replies received from the scientific experts can be found in Annex D. The written replies from the Codex Alimentarius Commission, JECFA and IARC can be found in Annex E-1, Annex E-2 and Annex E-3, respectively.

[376] See Annexes F-1, F-2 and F-4.

each other's comments on experts' replies and replies from international organizations. Parties provided these second rounds of comments on 12 July 2006.[377]

7.95 The Panel met with the six experts and four representatives from Codex, JECFA and IARC in the presence of the parties on 27-28 September 2006 in a meeting that was open for public observation through a closed-circuit television broadcast. In this meeting, Dr. Vincent Cogliano, Head of the IARC Monographs Programme, served both as an individual scientific expert and as the representative of the IARC. The other representatives were WHO JECFA Secretary Dr. Angelika Tritscher, FAO JECFA Secretary Dr. Annika Wennberg, and Codex Secretary Dr. Kazuaki Miyagishima. The meeting provided an opportunity for the parties and the Panel to ask questions to the experts and for the experts to clarify points that they had made in their written responses to the questions.[378] This meeting was followed by the Panel's joint second substantive meeting with the parties on 2-3 October 2006.

7.96 The Panel wishes to record its appreciation to the experts and the representatives of the international entities for their contributions. They were provided with large volumes of scientific materials and a limited timeframe to reply to a long set of questions. They were also requested to reply to extensive questions from the parties and the Panel during the two-day meeting in Geneva. They provided detailed and comprehensive responses. They provided the necessary scientific input to assist the Panel in understanding the issues raised by the parties and resolve the trade dispute before it. The clarity of their explanations and their professionalism were particularly appreciated by the Panel.

3. Other procedural issues

(a) Request by the European Communities that relevant scientific evidence and data be provided by Canada

7.97 In a letter dated 21 October 2005, the **European Communities** requested that Canada provide the scientific studies on the basis of which it conducted its risk assessments and approved the six hormones at issue for animal growth promotion so that the Panel, the experts and the European Communities could be given an opportunity to consider them.

7.98 **Canada** argued in a letter of 3 November 2005, that the Canadian measure at issue in these proceedings was Canada's *European Union Surtax Order*. Because the European Communities had challenged the WTO-consistency of Canada's measure, the issue of EC's compliance with the recommendations and rulings of the DSB in *EC – Hormones* had arisen. That was the reason for the Panel's inquiry into the EC's measure and conformity of that measure with the recommendations and the rulings of the DSB in *EC – Hormones*. The sanitary and phytosanitary measure at issue was that of the European Communities. It was the adequacy of the EC risk assessment that was relevant, not that of any other WTO Member. Therefore, in Canada's view, the EC request was inappropriate.[379]

7.99 In a letter to the Panel dated 8 November 2005, the **European Communities** argued that the scientific basis of the EC measure at issue was being challenged with reference to assessments done by other bodies or institutions, including the defending party's own regulatory bodies. If the Panel and the experts were to assess objectively the relevance and sufficiency of the scientific information on which the European Communities relied in order to ban these substances, they would have to review also the underlying evidence on which JECFA and some WTO Members relied in order to conclude that the hormones at issue were safe. Due process required that the Panel request the defending party to submit its underlying scientific studies.

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[377] See Annexes F-3 and F-5.
[378] A copy of the transcript of the meeting (hereafter the "Transcript") can be found in Annex G.
[379] Canada's letter of 3 November 2005.

7.100 In addition, the European Communities requested that the Panel ask Codex to submit to the Panel the underlying scientific evidence and data that served as the basis of the JECFA's assessments, which were invoked by the defending party in these proceedings. In the view of the European Communities, the Panel was competent to request the information at issue both from the defending party and from Codex under Article 13 of the DSU.[380]

7.101 **Canada** rebutted in its letter of 10 November that, although Canada referred extensively to the work of JECFA and the Codex Alimentarius Commission, the purpose was to show that there was indeed sufficient scientific evidence in respect of the five hormonal growth promotants concerned to allow the EC to perform an adequate assessment of risk. However, Canada did not cite the results of its own evaluation of the safety of the six hormonal growth promotants concerned in these proceedings, for the obvious reason that Canada's measure was not at issue. The issue here was whether the European Communities had performed a risk assessment in respect of oestradiol-17β that complied with the *SPS Agreement* and whether the European Communities had grounds to justify its position that there was insufficient scientific evidence in respect of the other five hormones to conduct an adequate risk assessment.[381]

7.102 The **European Communities** replied to the comments from Canada and the United States in a letter to the Panel dated 11 November 2005. The European Communities observed that a substantial amount of data on which JECFA based its findings came from, and were available only with, the United States' and Canada's authorities since JECFA had to rely exclusively on data provided to it, *inter alia*, by its members and the relevant industry. Thus, in the case of the six hormones in question, JECFA, where it did not base itself on scientific evidence publicly available, examined and relied on evidence that was available only with the United States' and Canada's regulatory authorities. Most of these studies were old and had never been published in peer reviewed scientific journals.

7.103 The European Communities added that, because the Panel had decided to examine the scientific basis of the EC compliance measure, this examination had to be carried out in the light of the assessments on which the responding party explicitly based itself in order to question the European Communities' risk assessment and continue its unilateral suspension of concessions, i.e. its own risk assessments and those of Codex/JECFA.

7.104 **Canada** argued in a letter of 21 November 2005, that the issues in these proceedings were simply (a) whether the European Communities could demonstrate that its ban on oestradiol-17β was supported by a risk assessment as required by Article 5.1 of the *SPS Agreement* and (b) whether its provisional ban on the other five hormones could be justified under Article 5.7 of that agreement. In Canada's view, nowhere in the *SPS Agreement*, the DSU or indeed the *WTO Agreement* as a whole was there a requirement that in assessing a Member's conformity with its obligations under the WTO Agreement, a panel may ask other disputing parties to justify their own measures that were not subject to dispute settlement. Were it to do so, the Panel would risk exceeding its jurisdiction.

7.105 Canada also argued that more importantly, the EC request was profoundly problematic from a systemic perspective. The Panel need not examine Canada's assessment of the safety of these hormones to make findings in this regard. Should the Panel accept the EC's request, this would have wide-ranging systemic implications for future WTO disputes, especially under the *SPS Agreement*, as Members challenging the WTO consistency of another Member's SPS measure could not do so without subjecting their own corresponding measure to scrutiny in the same proceedings. The EC's request would effectively impose an obligation on Members that challenge another Member's SPS measures to conduct their own independent risk assessments in respect of the challenged measures. This is nowhere set out in the *SPS Agreement*. Canada considered that creating this obligation would

[380] EC's letter to the Panel of 8 November 2005.
[381] Canada's letter of 10 November 2005.

be contrary to Article 3.2 of the DSU. It would also have obvious implications for all WTO Members, in particular for those that are developing or least developed countries and that do not necessarily have the kind of resources such risk assessment might require.[382]

7.106 The **Panel** considered the parties' arguments in its letter to the parties on the finalized working procedures for consultation with scientific and /or technical experts:

> "With respect to the EC's request that the Panel ask the US and Canada to provide the studies underlying the risk assessments of the US, Canada (and JECFA), the Panel is not in a position to fully assess the necessity for this information at this stage. This said, the Panel notes that its task is not to conduct a comprehensive assessment of the safety of hormones in meat. Rather, should the Panel consider it necessary for the resolution of the present dispute, it would assess the compatibility of the EC's measure with the provisions of the *SPS Agreement*. Nevertheless, to the extent that this information becomes necessary for the Panel to make its determination in this case, the Panel cannot exclude that it may request part or all of the information referred to by the EC. More generally, the Panel expects the Parties' full collaboration in gathering the information necessary for an objective assessment of the matter before it. The Panel also recalls that it is for each party to submit sufficient evidence in support of its assertions."[383]

7.107 In addition, the Panel wishes to recall its comments above on its discretionary power to seek information or not pursuant to Article 13 of the DSU. The Panel also agrees with the parties that, while it has to make an objective assessment of the matter before it, including an objective assessment of the facts, it is not supposed to make a *de novo* review of factual information, including scientific evidence, regarding the six hormones at issue. Thus, the Panel considered primarily in this context the measure taken by the European Communities to comply with the recommendations and rulings of the DSB in the *EC – Hormones* dispute. Having regard to the allocation of the burden of proof, the Panel deemed it appropriate to rely more particularly on the extensive amount of evidence submitted by the European Communities and Canada in their submissions. The Panel also took into account the opinions of the experts and the inputs from the international entities it consulted under Article 13 of the DSU. To the extent that the parties and the experts discussed the EC implementing measure in the context of the work of JECFA and Codex, the Panel believes that it was sufficiently informed to make an objective assessment of the facts and did not need to ask Canada and Codex to provide the information requested by the European Communities.

(b) Request by Canada to exclude materials not cited in the EC risk assessment as well as those published after the adoption of Directive 2003/74/EC

7.108 In a letter of 15 March 2006 commenting on the Panel's draft questions to experts, **Canada** expressed the view that, asking experts to provide information on scientific and technical issues that were neither considered in the assessment by the Scientific Committee on Veterinary Measures Relating to Public Health (SCVPH), nor by the European Communities itself when it adopted the measure would generate information that is unhelpful to the performance of the Panel's function.[384]

7.109 The **European Communities** stated that it had fundamental objections to the requests of the defending party. They were contrary to the Appellate Body's interpretation of the requirements of a "risk assessment", as set out in *EC – Hormones*. They were in violation of the Panel's Working

[382] Canada's letter of 21 November 2005.
[383] Panel letter to parties of 25 November 2005.
[384] Canada's letter to the Panel of 15 March 2006.

Procedures in this case, and they ran diametrically counter to the whole purpose of an expert consultation by the Panel.

7.110 According to the European Communities, the issue of whether a measure could be considered to be based on scientific evidence that was not cited or had not been taken into account in a risk assessment, or both, had already been settled by the Appellate Body in its report on *EC – Hormones*, at paragraphs 188 through 191. There the Appellate Body had dismissed the proposition by the complaining parties and the finding by the panel that scientific evidence had to be cited in the risk assessment, as a "minimum procedural requirement". The European Communities failed to understand why the defending party now re-opened an issue that had already been decided.

7.111 The European Communities had submitted new materials as exhibits in its replies to the Panel's questions and as part of its second written submission. They were, therefore, lawfully before the Panel and were directly covered by Paragraph 13 of the Expert Working Procedures.

7.112 According to the European Communities, the request of Canada had to be dismissed in view of the purpose of the experts' consultation. The principal objective of consulting experts was to provide the Panel with *objective* information and advice on questions related to the scientific basis of Directive 2003/74/EC. In order to fulfil this task, the experts could not ignore the most recent and directly relevant scientific evidence that is publicly available.[385]

7.113 On 31 March 2006, the **Panel** addressed this issue in its letter to parties informing the parties that it would not reject *a priori* any piece of evidence at that stage. However, the Panel decided to ask experts to specify whether their reply would have been different at the time of adoption of Directive 2003/74/EC and why. The Panel also requested the parties to identify, among the exhibits submitted, those studies to which they had had access before their publication date.

> "With respect to the issues raised in the letter of the United States on 14 March 2006, in Canada's comments of 15 March 2006, and in the European Communities' letter of 23 March 2006, the Panel is reluctant to reject a priori any piece of evidence at this stage. It will revert to this matter in its findings, as appropriate. In the meantime, and without prejudice to its final decision, the Panel has decided to amend some of its questions to the experts and request them to specify whether their reply would have been different at the time of adoption of the measure at issue (September 2003) and, if not, why.
>
> In this respect, the Panel would be grateful if the parties could specify by Friday, 7 April 2006, among the exhibits they submitted, those studies to which they had access before their official publication dates and, if so, specify the date on which they had access to each of them."[386]

7.114 Also, in its guideline letter sent on 30 March 2006 to the selected scientific and technical experts, the Panel specified that "wherever reference is made to scientific or technical facts, or comment is made on scientific evidence or literature, you are requested to provide references to the relevant studies and publications".[387]

7.115 The Panel considers that its approach allowed it to have a better understanding of the situation at the time of the adoption of Directive 2003/74/EC. However, since nothing has been submitted that became available subsequent to the adoption of the Directive and that differed in any fundamental

[385] EC's letter to the Panel of 23 March 2006.
[386] Panel letter to the parties of 31 March 2006.
[387] Panel guideline letter to selected experts of 30 March 2006.

way from the evidence available at that time[388], the Panel does not deem it necessary to address this issue any further.

(c) A new version of Exhibit EC-107, submitted by the European Communities on 29 May 2006

7.116 On 29 May 2006, the **European Communities** submitted a new version of its Exhibit EC-107, entitled "The sensitivity of the child to sex steroids: possible impact of exogenous estrogens", a study published on 2 May 2006. The European Communities stated that it would leave it to the Panel to decide whether to forward this version to experts.[389]

7.117 The **Panel** decided on 23 June 2006 not to forward this version of Exhibit EC-107 to the scientific experts for the following reasons:

> "With regard to the EC letter of 29 May and its attachment, the Panel takes note of the fact that the study submitted as Exhibit EC-107 has now been published. However, the Panel notes that the version of the study submitted as Exhibit EC-107 and the version attached to the EC letter of 29 May are somewhat different and that the difference are apparently not merely editorial. In this respect, the Panel recalls that the parties had been given until 21 December 2005 to submit factual evidence to the experts. Therefore, the Panel has decided not to send the published version of the study contained in Exhibit EC-107 to the experts."[390]

7.118 We confirm the position we took in this letter. We note that previous panels dealing with SPS measures have, in the context of proceedings under Article 21.5 of the DSU, considered *measures* adopted after the establishment of the panel.[391] However, as far as *evidence* is concerned, panels have generally refused to accept evidence submitted after a certain date, generally after the first substantive meeting, except for rebuttal purposes or upon a showing of good cause. In this particular case, the parties had been given until 21 December 2005, i.e. several weeks after their second written submissions, to provide factual evidence that they deemed relevant. The Panel considered also that submitting a modified study to experts at a relatively late stage of the expert consultation proceedings could generate confusion.

(d) Procedure for allowing the parties to comment on each other's replies to questions after the second Panel meeting

7.119 On 20 October 2006, the Panel, in line with the decision taken at the request of the United States in dispute WT/DS320, confirmed to parties that they would have an opportunity to comment on each other's replies to questions after the second Panel meeting. The deadline for such comments was 31 October 2006.[392]

(e) Request by the European Communities to be allowed to correct factual errors allegedly contained in the other party's comments on its replies to questions following the second Panel meeting

7.120 On 13 November 2006, the **European Communities** informed the Panel that it had studied the comments submitted by the United States and Canada on 31 October 2006 and had identified a

[388] This was confirmed by the experts when they were requested to specify in their replies to questions of the Panel whether their views would have been different at the time of the adoption of Directive 2003/74/EC.
[389] EC's letter to the Panel of 29 May 2006.
[390] Panel letter to the parties of 23 June 2006.
[391] See *Australia – Salmon (Article 21.5 – Canada)*, *Japan – Apples* (*Article 21.5 – US).*
[392] Panel letter to the parties of 23 October 2006.

number of inaccuracies and factual errors in their comments likely to affect the adjudication of the cases.

7.121 The European Communities requested that the Panel allow the parties to submit comments on the factual allegations contained in the comments on the responses. These comments would be restricted to factual matters and would not seek to further discuss any of the legal issues. This would enable the Panel to make an objective assessment of the facts and ensure a high quality panel report.[393]

7.122 **Canada** argued in a letter of 14 November 2006, that it had every confidence that the Panel would be able to make an objective assessment of the matter before it on the basis of the extensive submissions, replies to questions and comments on replies to questions that the parties had already made in this case.

7.123 Canada was concerned that, should the EC request prevail, it would lead to an endless loop of additional comments. In Canada's view, the EC knew what the procedure and the sequence of comments would be. It was a standard sequence in panel proceedings. The EC request was simply an attempt at this point to have the last word, rather than to correct any alleged inaccuracies in the record. Therefore, Canada requested the Panel to reject the EC's request and stated that, should the Panel decide to grant such additional chance to the EC for further comments, Canada would be entitled to comment on the EC's comments.

7.124 The **Panel** decided, on 20 November 2006, to reject the EC request:

> "Having carefully reviewed the arguments of the parties, the Panel does not consider it appropriate to offer them another opportunity to comment on alleged factual errors made by the other party. Procedurally, the Panel does not see any difference between comments on factual elements and comments on legal arguments; both can easily lead to endless discussions. The Panel is concerned that giving such an opportunity to parties could open the door to further delays in these proceedings since it would be difficult, once the Panel has allowed comments not foreseen in its timetable, to reject requests for additional comments on the other party's comments. At this juncture, the Panel believes that it has been sufficiently informed by the parties and the experts to be able to make an objective assessment of the case and deems it preferable to continue with the preparation of its report without further exchanges of comments between the parties. The Panel notes in this respect that the DSU provides opportunities for the parties to submit written comments, at a later stage, on the descriptive (factual and arguments) sections of the Panel Report and to request the Panel to review precise aspects of its Interim Report."[394]

7.125 The Panel does not deem it necessary to add anything to the reasoning above.

(f) Request by the European Communities for tape recordings of the transcript of the Panel meeting with scientific experts

7.126 On 31 January 2007, the **Panel** sent to the parties a draft written transcript of the hearing with the experts, for their review and comments.

7.127 On 14 February 2007, the **European Communities**, in the cover letter accompanying its comments on the transcript, requested the Panel to provide the parties with the tape recordings of the

[393] EC's letter to the Panel of 13 November 2006.
[394] Panel letter to the parties of 20 November 2006.

meeting with the experts for them to check the accuracy of the transcription of the experts' replies. The European Communities argued that the replies of some of the experts were not properly or not fully reflected in the transcript, but did not identify specific parts of the transcript where such errors allegedly occurred.[395]

7.128 The **Panel**, in a letter dated 19 February 2007, requested the European Communities to identify in the draft transcript the places where the European Communities believed the replies of the experts during the meeting had not been properly reflected. The Panel added that, once the information had been provided, the Panel itself would further review the draft and make appropriate corrections if necessary. The Panel added that the parties had until 5 April 2007 to submit such information.

7.129 The **European Communities** responded to the Panel on 28 February 2007, confirming that it was not in a position to identify in advance all the places where the transcript may not be entirely accurate, unless it was given copies of the tapes. The European Communities added that some of its doubts had already been pointed out by the United States and some more doubts existed as regards the statements by one expert and by the representatives of the WHO and JECFA. The European Communities also stated that the tapes had been provided to parties in the past in the *EC – Hormones*, the *EC – Asbestos* and the second *EC – Bananas* cases.[396]

7.130 The **Panel** replied that, to its knowledge, in circumstances similar to the present dispute, panels had never provided the tape recordings used in transcripts of meetings with scientific or technical experts to parties for review. As the Panel indicated in its message on 19 February to all parties, parties were welcome to identify any places in the draft transcript where they believed inaccuracies could exist and the Panel would further review the draft and make appropriate corrections if necessary.[397]

7.131 On 28 March, the **European Communities** replied that tapes of recordings had been provided previously upon request. In support of its allegation, it submitted a transmission slip of 21 April 1997 in the *EC – Hormones* panel procedure. The European Communities added that it was entitled to expect that tapes be provided in this case as well.

7.132 The European Communities also pointed out that the written transcript of the meeting of the Panel with the scientific experts had been sent with considerable delay to the parties for verification. In view of the time which had elapsed, it was very difficult to verify the transcript with the required degree of certainty, in the absence of the recordings.

7.133 The **Panel** sent to the parties an additional message on 18 April 2007, rejecting the EC request for tape recordings:

> "Since the latest message from the Panel to the parties on 26 March 2007, the Panel has received from the European Communities an additional communication on 28 March, indicating that tape recordings had been provided to the European Communities in the original *EC – Hormones* panel proceedings.
>
> The Panel subsequently received a letter from the Unites States indicating that the EC failed to mention that the transmission slip it submitted together with its 28 March letter is not related to the tapes of the expert meeting in the original *EC – Hormones* dispute because the date mentioned on that slip (7 January 1997) does not correspond

[395] EC's letter to the Panel of 14 February 2007.
[396] EC's e-mail to the Panel of 28 February 2007.
[397] E-mail of the Panel to the parties of 26 March 2007.

> to the date of the experts meeting (17-18 February 1997) in the original *EC – Hormones* dispute between the United States and the European Communities (WT/DS26).
>
> The Panel found that the meeting date mentioned on the slip provided by the EC was the date of the first substantive meeting of the panel in the original *EC – Hormones* dispute between the European Communities and Canada. The meeting with experts in the two disputes was jointly held on 17-18 February 1997, while the meetings with parties were held separately. After further verification, we can confirm that, to the best of our knowledge, the tape recordings of the experts meeting on 17 and 18 February in the two original *EC – Hormones* panels were never provided to the parties.
>
> The Panel recalls that the European Communities' request is based on its desire to check whether the experts' replies at the experts meeting have been accurately reflected in the transcript. Consistent with the practice of other panels, the Panel has invited the parties and the experts to verify the accuracy of their own interventions during the meetings. In addition, the Panel invited the parties to identify any places in the draft transcript where they believe inaccuracies could exist and the Panel was ready to review those portions of the transcript and make appropriate corrections if necessary.
>
> By 5 April 2007, a deadline date set by the Panel in its communication to the parties on 26 March 2006, none of the parties had identified any such inaccuracies.
>
> Therefore, on the basis of the above, the Panel does not deem it necessary to provide the tape recordings of the meeting with the experts to the parties."[398]

7.134 The **European Communities** sent another message to the Panel on 11 May 2007, commenting on the Panel's decision:

> "The European Communities appreciates the e-mail of the Panel of 18 April replying to our additional communication on 28 March, indicating that the tape recordings that had been provided to the European Communities in the original *EC – Hormones* panel proceedings were not from a hearing with scientific experts.
>
> In that case we did indeed receive (and still have in our archives) from the panel five tapes of 90 minutes each of the meeting held on 7 January 1997, which was indeed a meeting not with scientific experts. The point we were making is that since panels have provided the parties in the past tapes of a regular hearing, why is it not possible to provide the tapes of a hearing with scientific experts (where verification of what exactly was said is even more important)?
>
> More generally, panels send to parties the factual part of the draft report for verification (which is essentially done on the basis of the written submissions of the parties). The hearing with scientific experts is also part of the factual part of the report. So, one can expect that the tapes from such a hearing with scientific experts can also be sent for verification. This is all the more important in the case of a hearing with scientific experts, because it is impossible both for the scientific experts and the parties to take verbatim notes of a hearing that lasted two days and with the speed at which the oral exchanges take place in such hearing. Indeed, the scientific

[398] Panel letter to the parties of 18 April 2007.

> experts presumably did not take verbatim notes of what they said during the hearing and so they are in the same difficult position as the parties to remember what exactly they have said several months ago. For example, the European Communities has some doubts whether the following paragraphs of the draft report it has received reflect accurately what exactly has been said by the experts during the hearing on 27-28 September 2006: paragraphs 353, 386, 388, 390, 421-422, 500, 690, 706, 710, 719-720, 734, 779, 785, 891, 994, 1018, 1028. Furthermore, the European Communities considers that something may be wrong or missing between paragraphs 972 and 973 of the draft report.
>
> The European Communities respectfully requests the Panel to reconsider its position. If the Panel still feels unable to provide the European Communities with the tapes, it would ask the Panel to set out its reasons for refusing this request in the Report."

7.135 On 5 June 2007, the **Panel** informed the parties that the European Communities had not identified the relevant paragraphs in the draft transcript that it wanted the Panel to review before the deadline of 5 April 2007, as specified by the Panel in its earlier communication to the parties. At such a late stage, the Panel had every reason to disregard the request for review of the paragraphs identified by the European Communities in its letter of 11 May 2007. Nevertheless, as a matter of prudence, the Panel checked the relevant paragraphs in the draft transcript against the original tape recordings and did not find any discrepancy beyond minimal editorial adjustments. Therefore, the Panel saw no reason to reverse its decision not to provide tape recordings of the meeting with scientific experts to the parties for further review.

7.136 The Panel believes that the reasons for its decision not to provide tape recordings of the meeting with scientific experts were sufficiently described in its communications. It does not deem it necessary to elaborate on them any further.

4. Scope of the Panel's mandate

(a) The measure at issue and the claims of the European Communities

7.137 The matter before this Panel is the alleged failure of Canada to comply with the DSU and the GATT 1994 in response to the adoption and notification to the DSB of an alleged compliance measure by the European Communities in the *EC – Hormones* case.[399]

7.138 The measure at issue is the continued application by Canada, after the notification to the DSB of Directive 2003/74/EC by the European Communities, of its decision to apply, as from 1 August 1999, import duties in excess of bound rates by imposing a surtax on a number of products imported from certain member States of the European Communities[400] without recourse to the procedures under the DSU. This decision had been taken pursuant to an authorization granted by the DSB to Canada to suspend concessions and other obligations on 26 July 1999.[401]

7.139 In its request for establishment of a panel, the European Communities lists Articles I and II of the GATT 1994 and Articles 23.1, 23.2(a) and (c); 3.7, 22.8 and 21.5 of the DSU as having been breached by Canada. However, in its first written submission and subsequently, the European

[399] WT/DS48.

[400] *European Union Surtax Order*, SOR/99-317, adopted on 28 July 1999, Canada Gazette, Part II, Vol. 133, No. 17, 18 August 1999, at 2012-2016. WT/DS321/6.

[401] WT/DSB/M/65, p. 19.

Communities elaborates on the scope of those claims. More particularly, it divides its claims between a set of *main* claims and one *conditional* claim.[402]

7.140 The European Communities also specifies how its *main* claims of violation of the DSU should be addressed. The European Communities makes a first series of main claims, alleging a violation of Article 23 of the DSU and, more particularly, Article 23.2(a) read in conjunction with Articles 21.5 and 23.1 of the DSU. The European Communities also makes a second series of main claims, alleging a violation of Article 23.1, read in conjunction with Articles 22.8 and 3.7 of the DSU. In support of the second series of claims, the European Communities alleges that it enjoys a presumption of good faith compliance "which cannot be undermined by a unilateral and unsubstantiated determination by Canada."[403]

7.141 The European Communities adds in its first submission that Directive 2003/74/EC, which it claims implemented the recommendations and rulings of the DSB in the *EC – Hormones* case, is compatible with Article 5.1 and 5.7 of the *SPS Agreement*. However, there is no reference to provisions of the *SPS Agreement* in the EC request for establishment of a panel.

7.142 The *conditional* claim, that of a violation of Article 22.8 of the DSU *per se*, is "made in the alternative and only on the condition that the Panel does not establish any violation under Articles 23.1, 23.2(a), 3.7, 22.8 and 21.5 of the DSU".[404]

7.143 This *conditional* claim is, like the second series of main claims raised by the European Communities, based on the EC view that it has complied with the recommendations and rulings of the DSB in the *EC – Hormones* case by adopting Directive 2003/74/EC and properly notifying it to the DSB. The difference is that, under the conditional claim, the European Communities alleges actual compliance, and not that it should be presumed to have complied in good faith.

7.144 The EC implementing measure imposes a definitive import prohibition on meat and meat products from animals treated for growth promotion purposes with oestradiol-17β and a provisional ban on meat and meat products from animals treated for growth promotion purposes with testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate. The EC implementing measure is allegedly "based on a comprehensive risk assessment and, thus, is fully compliant with the DSB recommendations and rulings. In particular, [according to the European Communities and] as stipulated by the Appellate Body, the results of the risk assessment 'sufficiently warrant' the definite import prohibition regarding one of the hormones (Article 5.1 of the *SPS Agreement*), [footnote omitted] and provide the 'available pertinent information' on the basis of which the provisional prohibition regarding the five hormones has been enacted (Article 5.7 of the *SPS Agreement*)."[405]

(b) Are the indications provided by the European Communities on how it wants its claims to be addressed part of the mandate of the Panel?

7.145 As a preliminary remark, the Panel notes that, when dealing with the scope of panel terms of reference, panels and the Appellate Body so far addressed situations where panel requests were alleged to be insufficiently precise. In the present case, the EC request for the establishment of a panel, while not as explicit as the EC first written submission, explains in its section 2 ("The object of the dispute") some of the elements of the approach that the European Communities wants the Panel to follow. Yet, it does not outline its claims as was done in the EC first written submission. For instance, the request for the establishment of a panel lists Article 22.8 but it does not differentiate

[402] EC's first written submission, para. 8.
[403] EC's first written submission, para. 70.
[404] EC's first written submission, para. 133.
[405] EC's first written submission, para. 17.

between the main "systemic" claim relating to Article 22.8 (violation of Article 23.1, read in conjunction with Articles 22.8 and 3.7 of the DSU) and the conditional "direct" claim of violation of Article 22.8. Likewise, in the request for establishment of a panel, each provision is identified separately, without any terms like "read together with" or "read in conjunction with."

7.146 In *Korea – Dairy*, the Appellate Body defined the meaning of *claim* and *arguments* as follows:

> "By *claim*, we mean a claim that the respondent party has violated, or nullified or impaired the benefits arising from, an identified provision of a particular agreement. Such a *claim of violation* must, as we have already noted, be distinguished from the *arguments* adduced by a complaining party to demonstrate that the responding party's measure does indeed infringe upon the identified treaty provision."[406]

7.147 In the opinion of the Panel, the approach of the European Communities as developed in its first written submission does not amount to "arguments" insofar as it does not "demonstrate that the responding party's measure does indeed infringe upon the identified treaty provision". In fact, it does not purport to explain to what extent the EC claims are justified, but simply circumscribes their scope.

7.148 We further note that, in *US – Carbon Steel*, the Appellate Body stated that:

> "[I]n considering the sufficiency of a panel request, submissions and statements made during the course of the panel proceedings, in particular the first written submission of the complaining party, may be consulted in order to confirm the meaning of the words used in the panel request and as part of the assessment of whether the ability of the respondent to defend itself was prejudiced. Moreover, compliance with the requirements of Article 6.2 must be determined on the merits of each case, having considered the panel request as a whole, and in the light of attendant circumstances."[407]

7.149 The Panel is mindful that this statement was made in relation to a situation where the terms of reference were alleged not to cover specific claims. On the contrary, in the present case, the European Communities narrows the terms of reference of the Panel insofar as it requires a specific approach to the provisions allegedly breached. However, this statement equally applies in the present circumstances to the extent that the EC first written submission may be consulted in order to confirm the meaning of the words used in the request for establishment of a panel.

7.150 In that context, it can be considered that the approach to this case requested by the European Communities and contained in its first written submission is actually a clarification of the claims listed in its request for establishment of a panel and not arguments, and that it informs those claims.

7.151 We therefore conclude that the EC approach outlined in its first written submission is part of the Panel's terms of reference. One consequence is that since the claim of "direct" violation of Article 22.8 is made *in the alternative*, the Panel cannot and will not address it unless the European Communities fails to establish its main claims. The other consequence is that we should address the main claims as elaborated by the European Communities in its first written submission and subsequently.

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[406] Appellate Body Report on *Korea – Dairy*, para. 139.
[407] Appellate Body Report on *US – Carbon Steel*, para. 127.

(c) Meaning of "read together with" and "in conjunction with" in the EC submissions

7.152 The main or principal claims of the European Communities raise an additional question, i.e. whether the European Communities alleges a violation of Article 23 of the DSU alone or of all the provisions cited in its submission in support of its claim of violation of Article 23.

7.153 The Panel does not believe that the fact that the European Communities alleges a violation of Article 23 "read together with" or "in conjunction with" other provisions implies that the European Communities does not raise any claim under Articles 3.7, 21.5 and 22.8 of the DSU.

7.154 The Panel recalls that the request for establishment of a panel made by the European Communities refers to "Article 23.1; 23.2(a) and (c); 3.7; 22.8 and 21.5 of the DSU". Thus, having regard to the definition of a claim referred to above, examining the conformity of Canada's measures with Articles 3.7, 21.5 and 22.8 of the DSU is part of the Panel mandate.

7.155 The Panel notes the argument of Canada that, were the Panel to adopt the interpretation advanced by the European Communities of the interplay between Article 23 of the DSU "in conjunction with" the various Articles of the DSU cited by the European Communities in its two claims, it would either impose on Canada an obligation that finds no textual basis in the DSU or remove Canada's right to act in accordance with the DSB authorization to suspend concessions without further multilateral intervention by the DSB.[408] We recall that paragraph 1 of Article 31 of the Vienna Convention on the Law of Treaties, embodying the customary rules of interpretation of public international law referred to in Article 3.2 of the DSU, provides that:

> "A treaty shall be interpreted in good faith in accordance with the ordinary meaning to be given to the terms of the treaty in their context and in the light of its object and purpose."

7.156 The Panel does not exclude that there could be situations where the rights or obligations of Members could vary depending on which other provision a particular article of the DSU is read together with. However, either the terms of the provisions concerned interpreted in their ordinary meaning, in their context and in the light of the object and purpose of the treaty or the provisions support the claim, or they do not. Likewise, it is often the case that the violation of a particular provision will have consequences on the legality of the measure at issue under other provisions of the same or of other covered agreements.

7.157 We note that, in *US – Certain EC Products*, the panel stated that:

> "Since we have already concluded that the 3 March Measure constituted a measure taken to redress a WTO violation (covered by Article 23.1), we proceed to examine whether the same 3 March Measure violated the provisions of the sub-paragraph 2(c) of Article 23 of the DSU, as well as Articles 3.7 and 22.6 of the DSU."[409]

7.158 In other words, it would appear that the panel in *US – Certain EC Products*, even though it considered the effects of a finding of violation of one provision on the other – this is probably what it meant by "Article 23.1 together with Articles 23.2(c), 3.7 and 22.6 of the DSU" in the title of the section where the above quotation is found – nevertheless made findings of violation of each

[408] Canada's second written submission, para. 9.
[409] Panel Report on *US – Certain EC Products*, para. 6.36.

provision individually. We note that, likewise, the Appellate Body assessed the panel findings on each provision separately.[410]

7.159 While the European Communities seems to insist on the violations of Article 23, the Panel does not believe that the terms "read together with/read in conjunction with" were meant to limit its findings of violation to Article 23. Rather, the European Communities is seeking findings on all the provisions cited but, because of the broadly cast wording of Article 23, the European Communities seeks to circumscribe the context in which that violation is to be found. In other words, it wants us to articulate any findings of violation of Article 23 with the violations of Articles 21.5, 22.8 and 3.7 of the DSU.

7.160 The Panel concludes that the fact that the European Communities is seeking findings of violation of Article 23 "read together with" or "read in conjunction with" should not be understood as meaning that the European Communities exclusively claims a violation of Article 23. The Panel believes that its mandate includes Articles 21.5, 22.8 and 3.7 of the DSU.

(d) Conclusion

7.161 From the above we conclude that:

(a) the indications given by the European Communities on how it wants this case to be addressed (main claims and alternative claim) are part of the Panel's mandate;

(b) the indication by the European Communities that certain provisions referred to in its request for establishment of the Panel be "read together" or "in conjunction with" does not mean that the Panel is not expected to make findings on each of these provisions.

5. Approach of the Panel on the basis of its mandate

7.162 We are mindful of the EC position that this case is primarily about alleged violations of the DSU and, in particular, Article 23 thereof. We note in particular the EC argument that it brought this case because Canada refused to initiate a procedure under Article 21.5 of the DSU and did not agree to any other procedural arrangement.[411] We note that the European Communities also claims that Canada breaches Article 23 of the DSU read together with Article 22.8 because it failed to withdraw its suspension of obligations in spite of the EC removal of the measure found to be inconsistent with a covered agreement.

7.163 In our opinion, the EC claims of violation of Article 23.2(a) read together with Articles 21.5 and 23.1 are not premised on compliance by the European Communities with the DSB recommendations and ruling in the *EC – Hormones* case, whereas the claims of violation of Article 23.1, read together with Articles 22.8 and 3.7 of the DSU, are. Indeed, the EC claims of violation of Article 23.2(a), read together with Articles 21.5 and 23.1 of the DSU are premised on the fact that the respondent would have maintained a measure that could be deemed to be a "determination to the effect that a violation has occurred" without having recourse to dispute settlement in accordance with the DSU. Such a determination could take place whether or not the European Communities has complied with the DSB recommendations and rulings in *EC - Hormones*. Comparatively, the second series of EC claims is, to the extent that it includes Article 22.8, premised on the requirement that the respondent measure can "only be applied until such time as the measure

[410] Appellate Body Report on *US – Certain EC Products*, para. 106 *et seq*.

[411] See, e.g., EC's reply to Panel questions after the first substantive meeting, question 50, paras. 184-185.

found to be inconsistent with a covered agreement has been removed", as claimed by the European Communities. Thus, addressing the second series of main claims of the European Communities entails that we review the question of the presumed or actual compliance of the EC implementing measure with the DSB recommendations and rulings in the *EC – Hormones* case.

7.164 We believe that these two series of claims, as presented by the European Communities, are independent from each other and can be addressed completely separately. However, while we are free to structure the order of our analysis as we see fit[412], we see no reasons not to review the EC claims in the order followed by the European Communities in its submissions. We therefore proceed now with the first series of claims raised by the European Communities.

B. FIRST SERIES OF EC CLAIMS: VIOLATION OF ARTICLE 23.2(A) READ TOGETHER WITH ARTICLES 21.5 AND 23.1

1. Summary of the main arguments of the parties[413]

7.165 The **European Communities** argues that by maintaining its suspension of obligations, Canada is seeking redress of a perceived violation of the WTO Agreement. Pursuant to Article 23 of the DSU, any attempt to seek "redress" can take place only pursuant to the rules and procedures of the DSU. Canada's continued suspension of obligations is contrary to the specific prohibition of unilateral conduct set out in Article 23.2(a) of the DSU. Instead, Canada should have introduced a compliance procedure under Article 21.5 of the DSU. By not doing so, Canada has violated the specific prohibition of unilateral conduct set out in Article 23.2(a) of the DSU. This violation of Articles 23.2(a) and 21.5 constitutes at the same time a violation of Article 23.1 of the DSU.[414]

7.166 The European Communities, referring to the panel report in *US – Section 301 Trade Act*, notes that the following three conditions need to be fulfilled in order to find a violation of Article 23.2(a) of the DSU. First, given the "chapeau" of Article 23.2, it needs to be established that a Member is seeking to redress a WTO violation. In the opinion of the European Communities, this is the case in this dispute. Second, Article 23.2(a) of the DSU requires that a Member has made a "determination to the effect that a WTO violation has occurred." Such a decision need not have a specific form, and can be inferred from action. The suspension of concessions or other obligations is the very means (albeit of last resort) of reacting to a violation and therefore necessarily implies a decision that there is a violation. The multilateral determination at the origin of the current suspension of concessions by Canada was, however, made with respect to the measures previously applied by the European Communities. Logically, it could not and did not apply to the measures subsequently adopted and properly notified to the WTO by the European Communities. If Canada continues to apply the suspension of concessions and related obligations, it necessarily implies that it has unilaterally determined that there continues to be a violation. It has, in addition, explicitly said so.[415] Third, Article 23.2(a) of the DSU is violated if the determination is not made in accordance with the rules and procedures of the DSU or is not consistent with the findings of a dispute settlement organ. The DSU provides for a specific procedure, namely Article 21.5 of the DSU, to address the situation that Members disagree over the existence or consistency of measures taken to comply with the recommendations and rulings of the DSB.[416]

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[412] Appellate Body Report on *Canada – Wheat Export and Grain Imports*, paras. 126-129.

[413] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[414] EC's first written submission, para. 47.

[415] EC's first written submission, paras. 50-57.

[416] EC's first written submission, paras. 60-61.

7.167 In the view of the European Communities, there exists obviously a disagreement as to whether or not, by adopting Directive 2003/74/EC, the European Communities has implemented the recommendations and rulings from the DSB in the *EC – Hormones* case. Article 21.5 of the DSU requires that that disagreement *shall* be decided through recourse to dispute settlement. To date, Canada has refused to initiate a compliance procedure under Article 21.5 (or any other dispute settlement procedure under the DSU). Instead, it continues to apply the suspension of concessions and other obligations as if no "measure to comply" had been taken or the non-compliance of the new directive of the European Communities had already been multilaterally established.[417]

7.168 **Canada** argues that it is not seeking the redress of a violation within the meaning of Article 23.1 of the DSU. Canada considers that it already sought and obtained redress pursuant to the rules and procedures of the DSU for a violation by the European Communities of its WTO obligations. An action taken pursuant to a multilateral DSB authorization cannot amount to a unilateral determination. Thus Canada has in no way acted inconsistently with Article 23.1 of the DSU by failing to have recourse to, and abide by, the rules and procedures of the DSU.

7.169 Canada adds that its assessment concerning the consistency of the EC implementing measure is irrelevant to Canada's continued suspension of concessions. Canada's suspension of concessions is based on the ongoing validity of the DSB authorization of 26 July 1999 and not on any views it has developed on the consistency of the EC current measure.[418]

7.170 Canada further argues that, in this case, it has not made a unilateral determination in contravention of Article 23.2(a) of the DSU. According to Canada, it is clear from the text of that provision that it can only be seen to have made a unilateral determination where it is seeking the redress of a WTO violation.

7.171 Canada recalls that, in interpreting the meaning of the term "determination" in the context of Article 23.2(a) of the DSU, the panel in *US – Section 301 Trade Act* found that "a 'determination' implies a high degree of firmness or immutability, i.e. a more or less final decision by a Member in respect of the WTO consistency of a measure taken by another Member." On the basis of this interpretation, the Panel then specified that mere opinions or views expressed by a Member before that Member reaches the decision to seek redress of the inconsistency, are not intended to be covered by Article 23.2(a). Canada argues that, in the current case, it has not passed the threshold of a "determination" regarding the EC current measure. Canada recalls that, on several occasions it has stated that it was prepared to discuss with the European Communities the WTO consistency of its current measure.

7.172 Canada claims that it is the responsibility of the European Communities to establish that it has complied with the DSB's recommendations and rulings. In accordance with this view, Canada stated in the DSB that it sees no reason to initiate WTO procedures or to take any other action at this time.[419]

7.173 As far as the EC claim under Article 21.5 is concerned, Canada argues that the European Communities was perfectly free to have recourse to Article 21.5. In fact, in *EC – Bananas III (Article 21.5 – EC)*, it sought to do precisely that. Recourse to Article 21.5 of the DSU by the European Communities would have been the most appropriate mechanism under the DSU for obtaining a multilateral determination of compliance or non-compliance of the EC current measure. The European Communities' own failure to invoke this provision, however, is not a legitimate basis for a claim that Canada acted unilaterally by not invoking Article 21.5 of the DSU. Nor does it absolve the European Communities of its responsibility to demonstrate in appropriate procedures that

[417] EC's first written submission, paras. 62-66.
[418] Canada's first written submission, paras. 67-70.
[419] Canada's first written submission, paras. 71-75.

it has brought itself into compliance, should it wish to have the DSB authorization of Canada's suspension of concessions terminated.

7.174 Canada considers that, if the Panel were to adopt the EC's interpretation of the relationship between Articles 22.8, 23 and 21.5 of the DSU, Canada would be obliged in the current circumstances, on the basis of the EC unilateral and unproven assertions of compliance, to lift its suspension of concessions and initiate dispute settlement proceedings under Article 21.5. Such an interpretation would put into question a WTO Member's ability to rely on a validly obtained DSB authorization to suspend concessions and seriously undermine the proper functioning of the dispute settlement system in the WTO.

7.175 Canada considers that the European Communities is under an ongoing obligation to comply with the recommendations and rulings of the DSB. The EC unilateral declaration of compliance cannot somehow place the onus on Canada to launch proceedings under Article 21.5 of the DSU.[420]

7.176 According to the **European Communities**, the very fact of applying sanctions implies that a Member is seeking to redress a violation. And this in turn implies that this Member has made a "determination" about the WTO-inconsistency of the measure. The application of these sanctions may be justified if a measure by a Member has been properly found to be WTO-inconsistent and if, on that basis, the DSB authorizes the suspension of concessions. However, the European Communities asserts, the situation is different regarding the continuation of sanctions in the presence of a compliance measure which the DSB has not found to be WTO-inconsistent. A DSB authorization which has been granted in view of an original WTO-inconsistent measure cannot justify the continued application of sanctions against a different measure which has never been found multilaterally to constitute a WTO violation.[421] Rather, since the application of sanctions requires a causal relationship to a WTO-inconsistent measure it is clear that any present application of sanctions by Canada must be linked to a present EC measure, namely, its implementing Directive. Conversely, it is logically not possible to justify the present application of sanctions to a past and no longer existent measure. Thus, the continuation of the sanctions is a continuing act of "seeking redress". To accept Canada's argument would lead to the result that Canada could continue to apply sanctions irrespective of any events occurring after the DSB authorization.

7.177 The European Communities adds that, since Canada submits that the original purpose of its sanctions has not changed, it argues that the EC compliance measure is still inconsistent. This undermines the credibility of Canada's argument that it applies sanctions only because of the DSB authorization.

7.178 The European Communities considers that, regarding the notion of "seeking redress" under Article 23, Canada's action fits precisely into the jurisprudential definition that a Member act "in response to a perceived violation by another Member of that Member's WTO obligations". Since Canada has officially stated that it considers the EC compliance measure as WTO inconsistent and since it applies sanctions against a perceived violation (which in this case can only be the EC compliance measure since the original measure does not exist any more) the conditions of the above definition under Article 23 are fully met.

7.179 In this context, the European Communities considers that Canada has also met the threshold of a unilateral "determination" in violation of Article 23.2(a) of the DSU. The term "determination" has been elaborated by the panel in *US – Section 301 Trade Act* which considered that what is decisive under Article 23.2(a) is not so much whether an act constitutes a "determination", which was in the view of the panel "a more or less formal requirement that needs broad reading", but whether it

[420] Canada's first written submission, paras. 76-82.
[421] EC's first oral statement, paras. 27 *et seq.*

is consistent with the DSU rules and procedures. The European Communities concludes from this finding that even an implicit determination by the appropriate behaviour, such as the continuation of sanctions, would be covered by a "broad reading" of this requirement, in particular if the continuation occurs deliberately and is accompanied by statements.

7.180 In this respect the European Communities first notes that all relevant elements should be taken into account to assess whether a Member makes a unilateral determination of a violation when he seeks to redress a situation. Not every policy statement may be equal to a "determination" of a violation or made with the purpose of "seeking a redress of a violation" but, if a WTO Member repeatedly and consistently states that a violation by another Member exists and, in this context, this Member applies concrete measures against the other Member, it can be concluded that this Member is seeking a redress against a violation on the basis of a unilateral determination. Applying these principles to the present case, there can be no doubt that Canada has made a unilateral "determination" of non-compliance of the EC measure.

7.181 Second, the European Communities notes that, in addition to its recurrent statements regarding the WTO-inconsistency of the EC compliance measure, Canada continues to apply sanctions against the European Communities. Both its public statements and its actions are fully coherent and they demonstrate that Canada has indeed made a "determination" of an alleged WTO violation by the EC compliance measure.

7.182 The European Communities also sees merits in China's argument that the time-factor may be relevant for assessing when a "determination" actually has been made. The European Communities made a similar argument when pointing to the reasonable time frame in which an implementing Member can expect the other Party to bring an Article 21.5 proceeding. This argument does not ignore that this specific case raises complex scientific questions but up until now Canada had five years to consider these questions since the European Communities first notified its draft proposal to the SPS Committee.

7.183 According to the European Communities, Canada has not been able to offer any legal arguments on why the continued application of sanctions is not violating Article 21.5 in conjunction with Articles 23.1 and 23.2(a) of the DSU. The obligation to initiate a compliance review under Article 21.5 of the DSU is linked to Canada's continued application of sanctions against the EC compliance measure. Because of this, Canada is under a positive obligation to bring a compliance proceeding against the EC measure. By not doing so Canada violates Article 23 of the DSU. Thus, in this specific situation, Canada's discretion regarding whether or not it is appropriate to initiate WTO proceedings is limited as the failure to do so automatically encroaches on the EC rights not to be exposed to sanctions for a measure which another WTO Member unilaterally determines as WTO-inconsistent. Whereas a Member in violation of its WTO obligations is under an active obligation to comply, the retaliating Member is under an active obligation to initiate a compliance review under Article 21.5 of the DSU. Failure to do so will result in a violation of Article 23.1, 23.2(a), 21.5 of the DSU.

7.184 With respect to Canada's comments regarding a self-initiated Article 21.5 review by the European Communities, the European Communities recalls that it is not possible or meaningful to initiate a compliance review against its own implementing measure. The DSU is based on a contradictory proceeding whereby a complaining party alleges a WTO-violation against another party. Conversely, the DSU does not provide for a situation where a "complaining party" alleges the WTO-consistency of its own measure, in particular to prove the negative that is that its measure is *not* WTO-inconsistent.

7.185 **Canada** considers that Article 21.5 creates a right to initiate compliance proceedings, not an obligation. Nor can the other provisions of the DSU cited by the EC be interpreted to compel Canada,

in the circumstances of this case, to initiate proceedings to challenge the EC's purported implementing measure and to suspend the application of Canada's measure pending the outcome of that proceeding.

7.186 Canada notes that the European Communities admits that Article 23 of the DSU applies only when Members "seek redress" of a WTO violation. Canada is of the view that it cannot be found to be violating Article 23 of the DSU by continuing to suspend concessions in the absence of some intervention by the DSB that would either explicitly or implicitly terminate the DSB authorization. The fact that Canada continues to suspend concessions under such authority, even in the face of a purported implementing measure by the European Communities, does not render Canada's conduct inconsistent with Article 23 of the DSU. In these circumstances, Canada has taken no action to "seek redress" for any alleged WTO inconsistency of the EC implementing measure. The EC adoption and subsequent notification to the DSB of its purported implementing measure cannot change the legal basis of Canada's continued suspension of concessions.

7.187 Canada states that its continued suspension of concessions is not aimed at remedying any alleged violations of the EC implementing measure. Canada's conduct continues to be based on the DSB authorization and is therefore not based on Canada's views regarding the non-compliance of the EC's implementing measure. Consequently, Canada is acting in a manner fully consistent with Article 23 of the DSU.

7.188 Canada has not acted inconsistently with Article 23.2(a) of the DSU because it has not made a unilateral determination regarding the EC's implementing measure. Given that Canada is not "seeking redress" for perceived WTO violations of the EC implementing measure, Canada cannot have made a "determination" within the meaning of Article 23.2(a) of the DSU. The EC's claim in this regard must fail.

2. Reasoning of the Panel

(a) Introduction

7.189 The European Communities claims a violation of Article 23.2(a), read together with Articles 21.5 and 23.1. Article 23.2(a) contains specific obligations compared with Article 23.1. We therefore deem it relevant to address the violation of Article 23.2(a) first.[422]

7.190 Article 23.2(a) reads as follows:

> "2. In such cases, Members shall:
>
> (a) not make a determination to the effect that a violation has occurred, that benefits have been nullified or impaired or that the attainment of any objective of the covered agreements has been impeded, except through recourse to dispute settlement in accordance with the rules and procedures of this Understanding, and shall make any such determination consistent with the findings contained in the panel or Appellate Body report adopted by the DSB or an arbitration award rendered under this Understanding;"

[422] We note in this respect that, as mentioned by the Appellate Body in *Canada – Wheat Export and Grain Imports*, paras. 126-129:

> "As a general principle, panels are free to structure the order of their analysis as they see fit. In so doing panels may find it useful to take account of the manner in which a claim is presented to them by a complaining Member. Furthermore, panels may choose to use assumptions in order to facilitate resolution of a particular issue ..."

7.191 In order to decide whether Canada has or has not breached Article 23.2(a) in this case, the Panel must first find whether the determination was made "in such cases", i.e. when the conditions of Article 23.1 are met.

7.192 Article 23.1 reads as follows:

> "When Members seek the redress of a violation of obligations or other nullification or impairment of benefits under the covered agreements or an impediment to the attainment of any objective of the covered agreements, they shall have recourse to, and abide by, the rules and procedures of this Understanding."

7.193 In other words, the Panel must first establish whether Canada, in relation to the facts of this case, has been seeking redress of a violation of obligations or other nullification or impairment of benefits under the covered agreements, within the meaning of Article 23.1 of the DSU.

7.194 Thereafter, the Panel will proceed with determining whether Canada has breached Article 23.2(a). Once this is done, it will review the alleged violation of Articles 21.5 and 23.1, as necessary.

(b) "[S]eeking the redress of a violation of obligations or other nullification or impairment of benefits under the covered agreements" (Article 23.1 of the DSU)

7.195 Canada argues that it has taken no action to "seek redress" for any alleged WTO inconsistency of the EC implementing measure. The EC adoption and subsequent notification to the DSB of its purported implementing measure cannot change the legal basis of Canada's continued suspension of concessions. Canada states that its continued suspension of concessions is not aimed at remedying any alleged violations of the EC implementing measure. Canada's conduct continues to be based on the DSB authorization and is therefore not based on Canada's views regarding the non-compliance of the EC implementing measure.

7.196 We agree with Canada that Article 23.1 of the DSU is not breached when a Member's suspension of concessions or other obligations has been multilaterally authorized by the DSB, because the Member concerned "ha[d] recourse to, and abide[d] by, the rules and procedures of [the DSU]", within the meaning of Article 23.1. Indeed, Canada already sought redress against the original EC ban under the DSU.

7.197 In the opinion of the Panel, Article 23.1 applies in this case only with respect to a determination against a measure which has not yet been subject to a recourse to the rules and procedures of the DSU. We must therefore determine first whether Directive 2003/74/EC is such a measure.

7.198 We note the arguments of the European Communities that it adopted a new directive which it considers implements the recommendations and rulings of the DSB in the *EC – Hormones* case.[423] We first recall that Directive 2003/74/EC has never been as such subject to recourse to the rules and procedures of the DSU by Canada. For instance, no panel has been established at the request of Canada to review the conformity of Directive 2003/74/EC with the covered agreements. Second, Canada does not argue that Directive 2003/74/EC is identical to the measure that was found in breach of the *SPS Agreement* in the *EC – Hormones* case. The fact that both parties consider that the EC implementing measure is not the same measure as that which was found in breach of the WTO Agreement by the DSB in the *EC – Hormones* case is confirmed by the allegations they made in relation to that implementing measure before this Panel. The European Communities considers that

[423] EC's first written submission, para. 17.

its ban on oestradiol-17β is compatible with Article 5.1 of the *SPS Agreement*, whereas its ban on the other five hormones is justified by Article 5.7. Canada alleges, *inter alia*, the incompatibility of the ban on oestradiol-17β with Article 5.1, and of the provisional ban on the other five hormones with Article 5.7. These are different provisions than those invoked in the *EC – Hormones* case with respect to the same hormones.[424] Thus, by arguing as it does in this case, Canada implicitly acknowledges that the measure at issue is different from the original measure found in breach of the WTO Agreement both legally and in substance, even though an import ban on meat treated with hormones for growth promotion purposes is still applied.

7.199 We are aware of the fact that the original ban remains in force. We consider, however, that this is insufficient to conclude that Directive 2003/74/EC is not different from the measure originally found in breach of the WTO Agreement and should be deemed for that reason to have been subject to the rules and procedures of the DSU. We recall that it is not the ban on meat treated with growth promotion hormones as such that was found illegal in the *EC – Hormones* case, but the justification for this ban which was found insufficient. The European Communities is not prevented by the *SPS Agreement* from imposing any ban on import of meat treated with growth promotion hormones. The European Communities can impose such a ban provided it is compatible with the relevant requirements of the *SPS Agreement*. As a result, the Panel does not consider that the fact that the ban remains in place means that no new measure has been adopted.

7.200 Canada argues that its measure, taken on the basis of a DSB authorization, is by definition WTO-consistent. As Canada's measure is authorized by the DSB, it is the DSB that must determine whether the conditions exist for the termination of that authorization.[425] Canada adds that its continued application of a measure suspending concessions that is duly authorized by the DSB cannot at the same time be construed to be a conduct inconsistent with Article 23 of the DSU simply because the European Communities has adopted a measure that it, and it alone, now claims brings it into compliance.[426]

7.201 We agree with Canada that it was *authorized* by the DSB to suspend concessions and that this authorization has not been revoked. We note however, that this is only an *authorization*, not an *obligation* imposed by the DSB. The Panel agrees with the European Communities in this respect: "authorization by the DSB" does not mean "obligation to suspend concessions". This is confirmed by the practice under the DSU pursuant to which, in a number of cases where authorizations to suspend concessions have been requested, no suspensions was subsequently applied, in spite of the DSB authorization.[427] In other words, the fact that, after the notification of Directive 2003/74/EC, Canada continues to apply its suspension of concessions even though it has no obligation to do so is evidence that Canada is actively "seek[ing] the redress of a violation of obligations or other nullification or impairment of benefits under the covered agreements".

7.202 We note that the DSU does not provide for any procedure regarding the revocation of an authorization to suspend concessions. The adoption of a decision to revoke such an authorization by the DSB would require consensus[428], which would in turn require an absence of objection from the Member suspending concessions or other obligations, which may be difficult to obtain. We consider that this is not necessary, essentially because the DSB grants an *authorization*, which the Member

[424] In the original *EC – Hormones* dispute, the panel noted the European Communities had explicitly stated that its measures are not provisional measures in the sense of Article 5.7 of the *SPS Agreement*. See Panel Report on *EC – Hormones (Canada)*, para. 8.252.

[425] Canada's first written submission, para. 41.

[426] Canada's second written submission, para. 12.

[427] In the *Brazil – Aircraft* case, and *Canada – Aircraft Credits and Guarantees* case, the DSB authorized Canada and Brazil to suspend concessions, but neither of them applied the authorization. In *EC – Bananas III* case, Ecuador was authorized to suspend concessions but did not exercise that right.

[428] See Article 2.4 of the DSU.

concerned is free to apply or not. We also note that Article 22.8 of the DSU does not provide for any decision of the DSB for a suspension of concessions or other obligations to cease to apply. The first sentence of Article 22.8 simply provides that:

> "The suspension of concessions or other obligations shall only be applied until such time as the measure found to be inconsistent with a covered agreement has been removed, or the Member that must implement recommendations or rulings provides a solution to the nullification or impairment of benefits or a mutually satisfactory solution is reached." (Emphasis added)

7.203 In none of the circumstances foreseen by Article 22.8 does this provision require a decision of the DSB. In other words, it is for the respondent in this case to take appropriate steps to ensure that the suspension of concessions or other obligations is only applied until such time as foreseen in Article 22.8.

7.204 We also note that, pursuant to Article XVI:4 of the Agreement Establishing the WTO, Members must ensure the conformity of their laws, regulations and administrative procedures with their obligations as provided in the agreements annexed to the Agreement Establishing the WTO, including the DSU.

7.205 We conclude that Canada does not need a multilateral decision in order to terminate the suspension of concessions or other obligations for which it got authorization from the DSB.

7.206 For the reasons stated above, we consider that the EC implementing measure is, compared with the measure for which Canada was granted authorization to suspend concessions and other obligations by the DSB, a measure which has not been subject to a recourse to the rules and procedures of the DSU.

7.207 Canada, by maintaining its suspension of concessions even after the notification of the EC implementing measure, is seeking redress of a violation with respect to the EC implementing measure, within the meaning of Article 23.1 of the DSU. If it were not, as mentioned above, Canada would not have to maintain that suspension.

7.208 We now proceed to assess whether Canada breached Article 23.2(a).

(c) Violation of Article 23.2(a)

(i) Introduction

7.209 In order to assess whether Canada breaches Article 23.2(a), we must review the following conditions:[429]

(a) whether Canada made a determination that the EC implementing measure violates the WTO Agreement;

(b) whether Canada failed to make such determination through recourse to dispute settlement in accordance with the rules and procedures of the DSU; and assuming that it did,

[429] We note that a similar approach was applied by the Panel in *US – Section 301 Trade Act*, footnote 657.

(c) whether Canada failed to make any such determination consistent with the findings contained in the panel or Appellate Body report adopted by the DSB or an arbitration award rendered under this Understanding.

7.210 We will review these requirements successively.

(ii) Did Canada make a determination that the EC implementing measure violates the WTO Agreement?

7.211 We note that, in the present case, the European Communities notified its implementing measure on 27 October 2003.[430] At the DSB meeting of 7 November 2003 Canada made the following statement:

> "The representative of Canada said that the EC's communication to the DSB noted that the Directive 2003/74/EC "implements the WTO rulings" and the "... suspension of concessions to the EC by United States and Canada in this dispute are no longer justified". Canada had still seen no scientific basis for the ban. Health Canada had conducted a comprehensive review of the 17 new studies and had concluded that they did not provide any new scientific evidence that residues in meat from animals treated with steroid hormones – according to good veterinary practices – posed a threat to human health. Canada did not see any reason for WTO procedures at this time, but would welcome the opportunity for further discussion with the EC concerning the justification for its measures."[431]

7.212 Canada made another statement at the DSB meeting of 1 December 2003:

> "The representative of Canada said that, at the 7 November DSB meeting, Canada had put forward a suggestion for bilateral discussions concerning the justification for the EC's position that it had complied with the WTO ruling. However, the EC had not responded to Canada's suggestion for further bilateral discussions. Canada said that it was for the EC to establish that it had complied with the WTO rulings and continued to be open to discussions with the EC regarding its justification for its position. At this point, however, Canada did not see any basis for the removal of its retaliation measures nor for taking any other action."[432]

7.213 Article 23.2(a) refers to "a determination to the effect that a violation has occurred, that benefits have been nullified or impaired or that the attainment of any objective of the covered agreements has been impeded". Canada's position at the time of its statement before the DSB was clear as to the *scientific justification of the EC measure*, as illustrated by the following remark:

> "Canada had still seen no scientific basis for the ban. Health Canada had conducted a comprehensive review of the 17 new studies and had concluded that they did not provide any new scientific evidence that residues in meat from animals treated with steroid hormones – according to good veterinary practices – posed a threat to human health."[433]

[430] WT/DS48/20.
[431] WT/DSB/M/157, para. 31.
[432] WT/DSB/M/159, para. 24.
[433] WT/DSB/M/157, para. 31.

7.214 However, Canada did not expressly state that the EC implementing measure violated a covered agreement, or nullified or impaired benefits, or impeded the attainment of any objective of the covered agreements.

7.215 We recall that the Panel in *US – Section 301 Trade Act* defined a "determination" as follows:

> "[W]e consider that – given its ordinary meaning – a "determination" implies a high degree of firmness or immutability, i.e. a more or less final decision by a Member in respect of the WTO consistency of a measure taken by another Member."[434]

7.216 We will therefore proceed to determine whether other elements of Canada's statements or attitude could be evidence that Canada actually made a *determination* in respect of the *WTO consistency* of the EC implementing measure.

7.217 We first note that, given the importance of the scientific justification of the implementing measure for its conformity with the *SPS Agreement*, Canada's statement that it had not seen any scientific basis for the EC ban is quite close to stating that the implementing measure is not compatible with the *SPS Agreement*.

7.218 Second, this statement has to be read in conjunction with the other intervention of Canada at the DSB meeting of 7 November 2003 where Canada's representative stated that "he wished to clarify that he had stated officially that Canada was not removing the retaliatory measures."[435] Canada further clarified its position at the DSB meeting of 1 December 2003 where it mentioned that it "did not see any basis for the removal of its retaliation measures nor for taking any other action."

7.219 Canada did not specify that it saw no *legal* basis for the removal of its retaliation measures. However, this is implicit since Canada refers to "*any* basis", which means that it also saw no *legal* basis, in addition to no scientific basis, for removing the measure. Combined with Canada's statement about the scientific justification of the measure, this statement strongly suggests that Canada took a position on the WTO consistency of the implementing measure notified by the European Communities.

7.220 The next question is whether this constitutes a "determination" within the meaning of Article 23.2(a) of the DSU. The Panel is mindful of the definition of "determination" found in the panel report on *US – Section 301 Trade Act* and it is necessary to assess whether the consideration of the legality of the EC implementing measure as it results from Canada's statements is such that it can be reasonably deemed to convey, with a high degree of firmness and immutability, an apparently final conclusion as to the WTO compatibility of the EC measure.

7.221 The Panel first notes that nowhere in Canada's statements is there any indication that such statements were provisional, that Canada was still reviewing the EC implementing measure, or that it was expecting more information or planning to seek more information from the European Communities on the scientific justification of the measure. On the contrary, its conclusions as to the 17 studies are cast in definitive terms. As far as the legality of the implementing measure is concerned, the Panel notes that Canada *officially* stated that it was not removing the retaliatory

[434] Panel Report on *US – Section 301 Trade Act*, footnote 657.
[435] WT/DSB/M/157, para. 33.

measures and that is saw no basis for their removal or for taking any other action.[436] The Panel notes that there is no condition or qualification attached to these statements.

7.222 We note that the statements quoted above suggest that Canada was ready to engage into bilateral discussions concerning the justification for the EC position that it had complied with the WTO ruling and that Canada would have made a proposal to that effect at the DSB meeting of 7 November 2003. The Panel notes that, in response to one of its questions, the parties specified the extent of the consultations that took place after the notification of Directive 2003/74/EC. The Panel notes that they largely related to procedural issues.[437] In any event, even if Canada were ready to discuss the legality of the EC implementing measure, it officially stated that it was not removing its retaliatory measures, which has all the characteristics of a definitive decision. In the view of the Panel, since suspending concessions or other obligations is the consequence of the non withdrawal of a measure found to be WTO inconsistent[438], this statement implicitly meant that Canada had reached a decision that the EC implementing measure was not WTO consistent.

7.223 We therefore consider that Canada's statement meets all the requirements of the definition in the Panel Report on *US – Section 301 Trade Act* and that Canada made a "determination" within the meaning of Article 23.2(a).

7.224 Even if one were to consider that Canada's statements at the DSB were provisional comments, the subsequent continuation of the suspension of concessions by Canada without alteration and without saying that it was still studying the EC implementing measure is evidence that the statements before the DSB meant that Canada had no intention to remove its retaliatory measure, at least until further notice. We note in this respect that the term "determination" does not necessarily imply a formal decision[439], all the more so as such a formal decision was not necessary in order to continue the suspension of concessions. The continuation of the suspension of concessions corroborates the fact that Canada's statements before the DSB constituted a "determination" within the meaning of Article 23.2(a) of the DSU.

7.225 Canada argues that Article 23.1 and 23.2(a) cannot impose on Canada an obligation to have recourse to dispute settlement with regard to the EC implementing measure. According to Canada, this would deprive it, without any multilateral intervention, of its right to act in accordance with a validly obtained multilateral authorization to suspend concessions.

7.226 Canada adds that its continued application of a measure suspending concessions that is duly authorized by the DSB cannot at the same time be construed to be a conduct inconsistent with Article 23 of the DSU simply because the EC has adopted a measure that it, and it alone, now claims brings it into compliance.

7.227 As already mentioned above, the authorization to suspend obligation granted by the DSB is an *authorization*, not an unfettered right. Article 22.6 of the DSU has to be read in its context, which includes, *inter alia*, Articles 22.8, 23 and 3.7 of the DSU and Article XVI.4 of the WTO Agreement. Whereas the DSU could have envisaged a formal decision of the DSB to terminate an authorization to suspend concessions, this is not the case. Yet, the DSU provides that suspension of concessions "shall be temporary" (Article 22.8). Article 23.1 instructs WTO Members not to seek redress of a violation

[436] The two statements quoted above were also delivered by an official of the Canadian government at a formal meeting of a WTO body. There is no difference between that statement and any other statement where a formal decision of a Member is conveyed to the DSB.

[437] See parties' replies to questions after the first substantive meeting, question 50, Annex B-1, Annex B.3.

[438] See, *inter alia*, Article 3.7 of the DSU.

[439] Panel Report on *US – Section 301 Trade Act*, footnote 657.

without having recourse to, and abiding by, the rules and procedures of the DSU. Article 3.7 makes the possibility to suspend the application of concessions or other obligations subject to the authorization of the DSB. Article XVI.4 of the WTO Agreement requires that each Member ensure the conformity of its laws, regulations and administrative procedures with its WTO obligations. In other words, like in all aspects of public international law, WTO Members are expected to comply with their obligations under the DSU in good faith. This implies that a WTO Member may be called upon to take appropriate measures in the absence of any instruction from a multilateral body and even though it enjoyed until then the right to take other measures, if the circumstances change. This is the case with the suspension of concessions or other obligations if a Member notifies a measure which compatibility with the DSU has not yet been subject to a multilateral ruling under the rules and procedures of the DSU.

7.228 Indeed, the question before us in the context of Article 23.2(a) is not whether the European Communities has actually removed the measure found to be inconsistent, but whether it notified a measure which has not yet been subject to dispute settlement. As noted above, the European Communities notified a new piece of legislation and Canada itself recognizes that the measure is different and challenges its legality on different legal and factual grounds than it challenged the legality of the original measure for which it received an authorization to suspend concessions or other obligations from the DSB. Since this is a different measure, it is logical under Article 23 that Canada's prior authorization to suspend concessions or other obligation do not apply to this measure.

7.229 Canada considers that the EC argument that a notification of a new measure is sufficient to invalidate the DSB authorization to suspend concessions, if accepted, would allow the simple adoption and notification by one Member of a "compliance measure" automatically to render WTO-inconsistent an otherwise WTO-consistent measure of another Member. Under such a regime, a Member against whom suspension of concessions has been authorized could buy itself considerable periods of relief through the announcement of a measure that barely differed from the one originally found to be inconsistent with its WTO obligations. This would clearly not contribute to the objectives of inducing prompt compliance and ensuring the security and predictability of the multilateral trading system.

7.230 First, we believe that not only scam legislation, but also any other implementing measures could lead to recurrent litigations. One could envisage that, in a complex case, a Member could notify in good faith an implementing measure which would be subsequently found not to fully comply with the original recommendations and ruling of the DSB. This Member would have to submit a revised measure which could, once again, be challenged and found to comply only partly with the covered agreements. Such repeated inconsistencies could have to do with the fact that, pursuant to Article 19.1 of the DSU, panels and the Appellate Body may only recommend that the Member concerned bring its legislation into conformity with the covered agreement(s) found to be breached, and may only make non-binding suggestions regarding ways in which the Member concerned could implement their recommendations. Since Members remain free to implement recommendations and rulings as they deem appropriate, differences in the interpretation of the recommendations of the DSB cannot be excluded, which can result in old inconsistencies remaining in the implementing measure or in new ones creeping into it.

7.231 Second, we recall that our findings are limited to the facts of this particular case. In this case, the European Communities has adopted Directive 2003/74/EC at the outcome of a lengthy and complex internal decision-making process. The Panel notes in this respect that the Commission proposal was submitted in 2000 and 2001 and that the procedure for the adoption of the Directive was the procedure provided for in Article 251 of the Treaty establishing the European Community. This procedure involved a number of steps, including an Opinion of the European Parliament (1 February 2001), a Common Position of the Council of the European Union (20 February 2003) and finally a Decision of the European Parliament (2 July 2003), a Decision of the Council of the European Union

(22 July 2003) and an adoption by the European Parliament and the Council of the European Union on 22 September 2003.[440] Without prejudice to the question whether Directive 2003/74/EC is actually based on the three opinions of the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) of 1999, 2000 and 2002[441] within the meaning of the *SPS Agreement*, the Panel notes that this Directive expressly refers to those opinions[442] and that, as a result, they were part of the process that led to the adoption of the Directive. The Panel also notes the efforts of the European Communities to have the conformity of its measure reviewed under the DSU.[443] Even if the EC implementing legislation were ultimately found not to comply with the *SPS Agreement*, the Panel considers that it shows all the signs of an implementing measure having gone through all the formal process required for its adoption and showing, on its face, all the signs of a measure adopted in good faith.

7.232 We therefore conclude that Canada made a "determination" within the meaning of Article 23.2(a) in relation to Directive 2003/74/EC.

(iii) Did Canada fail to make such determination through recourse to dispute settlement in accordance with the rules and procedures of the DSU?

7.233 We note that Canada argues that it has not made any *determination* in respect of the EC implementing measure and therefore did not have to have recourse to the dispute settlement procedures of the DSU. However, we found above that it made a determination within the meaning of Article 23.2(a). Therefore, we conclude that Canada made a determination without having recourse to the DSU, thus breaching Article 23.2(a) of the DSU.

7.234 Canada also argues that it benefits from a multilateral authorization to suspend concessions in relation to the breach by the European Communities of the *SPS Agreement*, as a result of the recommendations and rulings of the DSB in the *EC – Hormones* case.

7.235 This is not the issue, however. The issue is whether the authorization to suspend concessions or other obligations granted to Canada under Article 22 of the DSU amounts to a multilateral determination of inconsistency of the EC *implementing measure* (i.e. Directive 2003/74/EC) with the covered agreements through recourse to the DSU. In our opinion, the answer is no.

7.236 We therefore conclude that Canada has not made any determination *through recourse to dispute settlement* in accordance with the rules and procedures of the DSU.

(iv) Did Canada fail to make any such determination consistent with the findings contained in the panel or Appellate Body report adopted by the DSB or an arbitration award rendered under the DSU

7.237 Since Canada has not made any determination through recourse to dispute settlement in accordance with the rules and procedures of the DSU, we conclude *a fortiori* that Canada has failed to make any such determination *consistent with the findings contained in the panel or Appellate Body report adopted by the DSB or an arbitration award rendered under the DSU*.

[440] See Directive 2003/74/EC, Preamble and footnote 3.

[441] Hereafter the "1999 Opinion", the "2000 Opinion" and the "2002 Opinion" or, together, the "Opinions".

[442] See Directive 2003/74/EC, whereas clauses 5 and 8.

[443] See EC's replies to Panel questions after the first substantive meeting, question 50, Annex B-1.

(v) Conclusion

7.238 For the reasons stated above, we find that Canada has breached Article 23.2(a) of the DSU.

(d) Violation of Article 21.5 of the DSU

7.239 We note that the European Communities claims that Canada should have had recourse to Article 21.5 of the DSU and that Canada's unilateral determination that the European Communities has not implemented the recommendations and rulings of the DSB is inconsistent with Article 21.5. Canada does not contest that the mechanism in Article 21.5 was available to the parties to obtain a determination under the DSU as to whether the EC measure is in compliance with the EC obligation. Canada argues, however, that it is not obligated to initiate a compliance procedure under Article 21.5.

7.240 We note that Article 23.2(a) provides that a determination must not be made "except through recourse to dispute settlement in accordance with [the DSU]". It does not specify which procedure under the DSU should be followed. While the procedure under Article 21.5 of the DSU could be one of the mechanisms available, in our view, the term "recourse to dispute settlement in accordance with the rules and procedures of this Understanding" encompasses any of the means of dispute settlement provided in the DSU, including consultation, conciliation, good offices and mediation.

7.241 The last proposition of Article 23.2(a) provides that such determination shall be consistent with the "findings contained in the *panel* or *Appellate Body* report adopted by the DSB or an *arbitration award* rendered under this understanding."[444] We do not consider, however, that that proposition *requires* that Members have recourse to a panel or to arbitration. In the opinion of the Panel, the last proposition of Article 23.2(a) only requires the Member *which decides to have recourse to a panel or to arbitration* to abide by the recommendation of the panel or the Appellate Body or the award of the arbitrator.[445]

7.242 As a result, we do not find it necessary to make a finding on whether Canada breached Article 21.5 by not having recourse to the procedure under that provision. Indeed, Canada did not have recourse to any procedure under the DSU with respect to the EC implementing measure (Directive 2003/74/EC) Under those circumstances, we deem it sufficient to limit our findings to Article 23 and exercise judicial economy with regard to the EC claim under Article 21.5 of the DSU.

(e) Violation of Article 23.1 of the DSU

7.243 Since we found that Canada has sought the redress of a violation with respect to the EC implementing measure (Directive 2003/74/EC) and made a determination without having "recourse to dispute settlement in accordance with the rules and procedures of [the DSU]" within the meaning of Article 23.2(a), we conclude that Canada failed to "have recourse to, and abide by, the rules and procedures of [the DSU]", in breach of Article 23.1 of the DSU.

3. Conclusion

7.244 On the basis of the above, the Panel concludes that Canada has violated Article 23.1 and 23.2(a) of the DSU by seeking redress of a violation of the WTO Agreement through a determination that the EC implementing measure did not comply with the DSB recommendations and rulings in the

[444] Emphasis added.

[445] Comparatively, there was no need for the negotiators of the DSU to refer to compliance with the results of consultations, mediation, conciliation or good offices since the results of such means of dispute resolution have, by their very nature, to be accepted by the parties.

EC – Hormones case without having recourse to dispute settlement in accordance with the rules and procedures of the DSU.

C. SECOND SERIES OF EC CLAIMS: VIOLATION OF ARTICLE 23.1, READ TOGETHER WITH ARTICLES 22.8 AND 3.7 OF THE DSU

1. Summary of the main arguments of the parties[446]

7.245 The **European Communities** argues that Canada is violating its obligations under Article 23.1, read in conjunction with Articles 22.8 and 3.7 of the DSU, by continuing to suspend concessions and related obligations even though the European Communities has taken and notified to the DSB the measures to implement its obligations and these measures have not been found WTO-inconsistent in an Article 21.5 procedure.

7.246 The European Communities adds that, in order to demonstrate that Canada is in violation of Article 23.1, read together with Articles 22.8 and 3.7 of the DSU, it is not required to explain in full the substance of its compliance measure and why this measure implements the DSB recommendations and rulings. Rather, the European Communities relies on the presumption of good faith which cannot be undermined by a unilateral and unsubstantiated determination by Canada.

7.247 The European Communities considers that, under Article 23.1 of the DSU, Canada is obliged to have recourse to, and abide by, the rules and procedures of the DSU which encompass, *inter alia*, Articles 22.8 and 3.7 of the DSU. According to these provisions, Canada is obliged not to apply any longer the suspension of concessions and related obligations after the inconsistent measure has been removed by the European Communities.

7.248 According to the European Communities, the authorization to suspend concessions or other obligations is a last resort, temporary measure and one of its main objectives is to induce compliance by the violating WTO Member. This objective entails, however, that once a Member has adopted compliance measures which are not properly challenged by the complaining Member, the suspension of concessions or other obligations can no longer be applied. Indeed, in such a scenario the suspension of concessions or other obligations would be deprived of one of its main objectives, i.e. to achieve implementation of a DSB decision, for the simple reason that the WTO Member has already taken measures to implement the DSB recommendation.

7.249 The European Communities acknowledges that Article 22.8 of the DSU does not specify how the removal of the WTO inconsistency is determined. However, in the light of its context, i.e. Articles 21.5 and 23.2(a) of the DSU, and given the exceptional nature of countermeasures, it is clear that a Member cannot unilaterally determine that the WTO inconsistency persists despite the notification of a compliance measure. Likewise, a Member cannot decide to continue to suspend concessions or other obligations unilaterally.

7.250 According to the European Communities, the WTO inconsistency of the implementing measure can only be determined in accordance with the appropriate procedure, namely Article 21.5 of the DSU.[447] Unless such a procedure concludes that the compliance measure does not fully implement the DSB recommendations and rulings, it cannot be presumed that this is the case. This also follows from the general principle of good faith as it applies in international State relations, under which States are normally considered to act in conformity with their obligations. This principle has been

[446] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[447] EC's first written submission, para. 84.

recurrently recognized in WTO jurisprudence. This principle constitutes one of the cornerstones of the WTO dispute settlement system. Thus, unless it is proven in accordance with the rules and procedures under the DSU that a WTO Member violates its commitments, this Member has to be considered to act in conformity with its WTO obligations. The presumption of good faith also applies for implementing measures. In application of this principle, Canada could not unilaterally determine that the European Communities implemented the DSB recommendations and rulings in a WTO inconsistent way. To the contrary, the European Communities must be presumed to have complied with its WTO obligations, if Canada refuses to establish the contrary.

7.251 According to the European Communities, whether a Member suspends for the first time concessions or other obligations or wishes to maintain the suspension despite an implementation act does not make a difference. In both cases, a Member must not substitute unilaterally its assessment of a WTO inconsistency of an implementation measure to the procedures under the DSU.

7.252 In the view of the European Communities, these fundamental principles are not altered by the fact that there exists a DSB authorization under Article 22.7 of the DSU to suspend concessions or other obligations. The DSB authorization cannot change the fundamental rules under the DSU. Rather, the DSB implements these rules. Thus, as the DSU provides that the suspension of concessions or other obligations should not be applied unless a WTO violation by a Member's measure has been properly established, the DSB authorization cannot be interpreted to justify such a suspension if a WTO violation of a Member's (new) measures has not been properly determined.

7.253 According to the European Communities, the basis for a DSB authorization to suspend concessions or other obligations is a prior *multilateral* determination that the implementing WTO Member has failed to comply with its obligations. This is the case if an Article 21.5 proceeding concludes that the implementing measure was insufficient. This is also implicitly the case if a Member has not adopted any implementing measure at all at the time of the DSB decision under Article 22.7 of the DSU.

7.254 Conversely, the European Communities argues, if a WTO Member implements properly its obligations after the DSB has authorized the suspension of concessions or other obligations the basis for this decision changes fundamentally. As the original DSB authorization was taken in view of the original measure, it cannot logically encompass the new implementing measure. Hence, the DSB authorization cannot cover the continued application of the suspension of concessions or other obligations, if a WTO Member subsequently implements its obligations in the absence of a multilateral review regarding the compliance (or not) of this new measure.

7.255 The European Communities adds that Canada's violation of Article 23.1 and Article 22.8 of the DSU necessarily entails a violation of Article 3.7 of the DSU. As Article 3.7 of the DSU contains the basic principles for the application of the suspension of concessions or other obligations, it follows that once a Member violates Article 23.1 read in conjunction with Article 22.8 of the DSU it necessarily also acts contrary to Article 3.7 of the DSU.[448]

7.256 **Canada** argues that the failure of the European Communities to comply within the reasonable period of time it had been granted gave Canada the right to seek authorization from the DSB to suspend concessions and subsequently to suspend concessions once that authorization was granted. However, the European Communities remains subject to an ongoing obligation to comply with its WTO obligations, including those requiring it to comply promptly with the recommendations and rulings of the DSB.

[448] EC's first written submission, paras. 67-123.

7.257 Canada considers that its measure, taken on the basis of this authorization by the DSB, is by definition WTO-consistent. As Canada's measure is authorized by the DSB, and remains under the surveillance of the DSB, it is the DSB that must also determine whether the conditions exist for the termination of that authorization. Any mechanism for terminating the authorization that is not under the authority and surveillance of the DSB undermines the ability of the dispute settlement system to achieve one of its central objectives, that of ensuring the security and predictability of the multilateral trading system.

7.258 Canada argues that, on the basis of the foregoing, the Panel must find that the DSB authorization permitting Canada to suspend concessions to the European Communities remains in effect and, as a result, that Canada's measure is not inconsistent with its obligations under any provision of the DSU.

7.259 According to Canada, as it is the European Communities that now seeks to have Canada's authorized measure "de-authorized", it is the EC that bears the burden of demonstrating to the DSB that the measure should no longer be authorized, by virtue of some action it has taken to comply. This is a necessary conclusion that flows from the general rule concerning the burden of proof, which states that the party asserting a particular claim has the burden of proving it.[449]

7.260 Canada notes that the European Communities may have had recourse to proceedings initiated under Article 21.5; there is nothing inherent in the wording of Article 21.5 that would prevent recourse to it by a Member that wishes to confirm the actual compliance of its measure and have the DSB authorization terminated by the DSB. Alternatively, the European Communities may initiate new proceedings in which it requests the Panel to determine the actual compliance of a measure it has adopted to implement the recommendations and rulings of the DSB. If the European Communities is successful in persuading the Panel that is has indeed complied, the result would be a recommendation to the DSB to terminate the DSB authorization. In either scenario, and in the absence of a mutually satisfactory solution, the continued suspension of concessions by Canada remains authorized and WTO-consistent until the European Communities initiates WTO proceedings, successfully demonstrates the actual compliance of its own measure, and has the DSB terminate the original authorization.

7.261 Canada is of the view that the EC allegations of violation of Articles 22.8 and 3.7 of the DSU by Canada not only ignore the ongoing existence of the DSB authorization and the European Communities own responsibilities, they are also based on an unsupportable assertion that the current EC measure benefits from a presumption of compliance.

7.262 Canada does not disagree with the European Communities on the temporary nature of the suspension of concessions. Canada accepts that, in the absence of a mutually satisfactory solution, it may only maintain its suspension of concessions until such time as it receives confirmation from the DSB that its efforts at inducing compliance have been successful, that the EC has in fact implemented the recommendations and rulings of the DSB in *EC – Hormones* and that, as a result, the DSB authorization has been terminated. Canada rejects, however, the EC assertion that somehow the period provided for in Article 22.8 has passed in these circumstances and that the suspension of concessions previously authorized by the DSB must now be ended.

7.263 Canada disagrees with the EC contention that its measure should benefit from a presumption of compliance in these particular circumstances. This dispute does not concern an EC measure taken as part of its regular day-to-day business of governing, prior to the engagement of the WTO dispute settlement mechanism. Nor does it concern a measure that the EC has taken to comply within the reasonable period of time, and prior to the adoption of DSB authorization to suspend concessions.

[449] Appellate Body Report on *US – Wool Shirts and Blouses*, DSR 1997:I, p. 323 at 333-338.

Any measure taken by the European Communities in either of these scenarios would be presumed to comply with its international obligations unless otherwise challenged. Rather, the dispute before this Panel concerns the failure of the European Communities to correct, within the reasonable period of time, a measure that had been found by the DSB to be inconsistent with the WTO obligations of the European Communities, and as a result the DSB authorized Canada to suspend concessions.

7.264 According to Canada, the European Communities' attempt to have its measure treated as if it had been adopted within the reasonable period of time, and prior to the adoption of the DSB authorization, ignores the legal reality of the current circumstances. Contrary to the EC's claims, there is very good reason to assume that the legal situation is not identical to that which prevailed prior to the adoption of the DSB authorization. The existence of the authorization by the DSB of Canada's measure distinguishes this case from those situations in which a general presumption of compliance would apply to the EC measure.

7.265 In Canada's opinion, the DSU does not explicitly address how a DSB authorization of suspension of concessions, once granted, is to be terminated. The European Communities itself acknowledges this point, but not its implications. In the absence of a specific provision setting out a mechanism, the DSU must be interpreted in such a way that each of its provisions can be given effect that is consistent with the object and purpose of the DSU.

7.266 Canada notes, on the one hand, a measure taken by the European Communities to comply would benefit from a presumption of compliance prior to the adoption by the DSB of an authorization to suspend concessions. On the other hand, a measure taken by Canada to suspend concessions on the basis of that authorization is in actual compliance with its WTO obligations. The adoption by the European Communities of a measure that it considers to implement its WTO obligations cannot, in itself, revoke the DSB authorization; in the absence of revocation by the DSB, that authorization still stands. As a result, any presumed compliance that the EC's measure would enjoy prior to the adoption of the DSB authorization must yield to the actual compliance of Canada's measure suspending concessions.

7.267 According to Canada, accepting any other interpretation of the relevant provisions of the DSU would undermine the objective of the dispute settlement system to ensure the security and predictability of the multilateral trading system.

7.268 As far as the EC allegation of violation of Article 3.7 is concerned, Canada argues that since Canada has demonstrated that it has not acted inconsistently with Article 22.8, the EC claims related to Article 3.7 must also fail.[450]

7.269 The **European Communities** does not deny that the DSB authorization has not formally been withdrawn. However, under Article 22.8 of the DSU it does not matter whether the DSB authorization has formally been removed or not. Rather, what matters is whether the suspension of concessions and related obligations may still be "applied" (pursuant to a DSB authorization). Article 22.8 of the DSU unequivocally provides that the suspension of concessions and related obligations may only be "applied" until the inconsistency of the measure has been removed.

7.270 According to the European Communities, Canada completely ignores this difference between the "existence" of a DSB authorization and the "application" of the suspension of concessions and related obligations (pursuant to that DSB authorization). Canada presents the European Communities' case to mean that the DSB authorization would be "withdrawn", "revoked" or "terminated". Yet, for the purpose of Article 22.8 of the DSU, the status of the DSB authorization does not matter.

[450] Canada's first written submission, paras. 37-65.

7.271 Furthermore, the European Communities emphasizes the self-executing nature of Article 22.8 of the DSU. The termination of the application of sanctions under this provision does not depend on a specific finding of the DSB or a withdrawal of the DSB authorization. Rather, once the conditions under Article 22.8 of the DSU are met – including in the presence of an unchallenged compliance measure – the application of suspension "shall" stop.

7.272 The European Communities argues that Canada's theory regarding the reversed burden of proof is rooted in the misconception that otherwise the DSB authorization would be terminated merely on the basis of a presumption of good faith compliance. As already mentioned, the question under what conditions the DSB authorization may be terminated is not the issue in this dispute.

7.273 The European Communities notes that Canada's theory has no basis either under WTO law or under public international law. The WTO jurisprudence is clear that the party bearing the burden of proof is the one that asserts the *affirmative* of a claim or defence. Furthermore, the burden of proof is one concrete example of the general good faith principle, i.e. the presumption of compliance. This principle applies to an implementing measure as such but not to a specific timing when the measure had been adopted.

7.274 According to the European Communities, Canada's argument about security and predictability could be understood to mean that the only secure and predictable way under the DSU is the application of sanctions as such. However, the application of sanctions under the DSU is not an objective in itself. The application of sanctions is designed to achieve another, higher objective, i.e. full compliance with the WTO obligations by another Member. Thus, if a violating Member has adopted compliance measures in good faith, it is indeed a matter of security and predictability of the trading system that the application of sanctions ceases to apply, if these measures are never properly challenged. If an implementing Member could not have the expectation that the sanctions would end the security and predictability of the WTO Agreement were indeed put at risk because this might reduce the incentive for an implementing Member to comply.

7.275 Finally, the European Communities would address Canada's theory regarding the way a DSB authorization may be terminated. The DSU does not provide for any procedure on how a DSB authorization could be formally terminated, and the idea of an implicit revocation is baseless. What the DSU, however, provides is until when the suspension of concessions may be "applied".[451]

7.276 **Canada** argues that in circumstances where concessions have been suspended on the basis of an authorization by the DSB, and where no mutually satisfactory solution has been reached, the onus is on the Member originally found to be non-compliant to take steps to confirm multilaterally that it has satisfied at least one of the conditions of Article 22.8 if it wishes to have the suspension of concessions no longer applied. Without such multilateral confirmation, the DSB authorization remains in effect and continues to authorize the suspension of concessions by the original complaining Member. This right to continue to suspend concessions is unaffected by any views the original complaining Member may develop and express regarding the actual compliance of the other Member's implementing measure.

7.277 Canada considers that the 2003 Directive simply amends the 1996 Directive. It is also clear that the EC attempt to comply is after the reasonable period of time that it was granted to do so. The European Communities cannot escape the consequences that its status of non-compliance, or late compliance as the case may be, in the previous dispute has on its rights and obligations at issue in this dispute.

[451] EC's second written submission, paras. 42-63.

7.278 Canada argues that it has not transferred the application of the authorization from the "old" inconsistent measure to a "new" unconfirmed measure. It is simply that Canada neither agrees nor has received multilateral confirmation that the European Communities has brought itself into compliance. In the absence of either of these circumstances being met, Canada is entitled to continue to rely upon the authorization.

7.279 According to Canada, the question is not when, whether and how the DSB authorization is terminated, revoked or ceases to have effect, but rather which party bears the burden of confirming the compliance of the implementing measure. The requirement that the European Communities bear this burden if it wishes to have the suspension of concessions ended is simply the logical consequence of the position in which it has placed itself in the EC – Hormones dispute.

7.280 Canada is of the view that Article 22.8 of the DSU cannot be "self-executing" in the light of the overall regime of surveillance established by the DSU in circumstances of non-compliance. In the light of the object and purpose of the DSU, and in the context of the other provisions relating to non-compliance, Article 22.8 requires multilateral confirmation that the conditions precedent have been satisfied before the suspension of concessions can no longer be applied. Most importantly, the authorization to suspend concessions as a result of a failure to comply within the reasonable period of time is granted solely by the DSB. The legal consequence of the combination of the ongoing DSB surveillance of non-compliance, the multilateral nature of the authorization and the reliance on that authorization by the original complaining Member is that a subsequent, unconfirmed claim that one of the conditions of Article 22.8 has been met is insufficient on its own to displace the multilaterally-agreed surveillance regime, regardless of how much effort is put into the measure underlying the claim.

7.281 According to Canada, in arguing that it has complied in good faith, the European Communities confuses several distinct issues related to "good faith" and "bad faith". The linkage made by the European Communities between the two should be rejected. The issue before this Panel is not whether the European Communities acted in "bad faith" when it adopted the 2003 Directive. It is, in the first instance, whether the 2003 Directive should be presumed to bring the EC 1996 Directive into compliance, and if such a presumption should not apply, whether the 2003 Directive actually does bring the EC 1996 Directive into compliance. As the Appellate Body has made clear, a finding that a Member does not comply with its WTO obligations – not to mention a mere investigation into whether or not it does – amounts to neither an accusation nor a finding of "bad faith". Similarly, an interpretation of the DSU that would deny the European Communities a presumption of compliance cannot be equated to a finding that it is presumed to have acted, or that it did act, in bad faith. The European Communities can make bona fide efforts to comply with its obligations and still not in the end succeed in complying. The principal issue in a review of the EC claim of compliance is not whether the European Communities should be presumed to have acted in good faith, but rather it is whether the European Communities has actually complied. In these circumstances, since Article 22.8 cannot be self-executing, the European Communities cannot benefit from a presumption of compliance and must instead demonstrate this compliance.

7.282 Canada adds that, ultimately the Panel should consider whether the adoption of a measure in one Member can be allowed to automatically render WTO-inconsistent a measure of another Member, without some intervening international act. The simple answer is no. Any other interpretation of Article 22.8 would allow a unilateral act to supplant a multilateral act, an outcome clearly not provided for in the DSU.

7.283 Canada considers that the European Communities places considerable emphasis on the distinction between the "termination/revocation" of the authorization, on the one hand, and the fact that the suspension of concessions may "no longer be applied", on the other. By focusing on such

formalities related to the termination of the authorization, the European Communities is attempting to distract the Panel from the EC substantive obligations arising out of the *EC – Hormones* dispute.

7.284 Canada notes that while no specific provision in the DSU requires the formal revocation of the DSB authorization, that does not mean that there cannot be, or should not be, an act by the DSB that is equivalent to revoking the authorization, whether that is implicit or explicit. Since the "multilateral confirmation" of compliance required before Article 22.8 can be given effect would generally come in the form of adoption by the DSB of panel findings of compliance, "confirmation" of compliance and the "revocation" of the authorization are essentially the same act of the DSB. The "revocation/termination" of the DSB authorization can therefore be either implicit or explicit. It would be implicit if the DSB simply adopted a panel's findings of compliance without addressing the issue of the status of the authorization. It would be explicit if the DSB specifically noted that as a result of its confirmation of compliance, its previous authorization no longer was in effect.

7.285 According to Canada, it is the EC's prerogative to choose to confirm its compliance in proceedings de novo, such as in these proceedings, in order to have the DSB authorization removed. The key issue in such proceedings is that the European Communities bears the initial burden of demonstrating that it has indeed brought itself into compliance for the Panel to find that the DSB authorization should cease to have effect. Now that the European Communities appears to have accepted that burden here, the main objective of these proceedings should be a review of the compliance of the EC measure with the recommendations and rulings of the DSB in EC – Hormones.[452]

2. Approach of the Panel

(a) Duty of the Panel to make an objective assessment of the matter before it

7.286 In light of the EC statement that this case is about procedural violations under the DSU[453], and in view of our findings above, we could normally exercise judicial economy and complete our review of this case at this juncture. Indeed, we found that Canada committed a procedural error under the DSU, breached Article 23.1 and 23.2(a) and should have had recourse to dispute settlement in accordance with the rules and procedures of the DSU if it wanted to seek redress of a violation of the WTO Agreement through a determination of violation of the WTO Agreement with respect to Directive 2003/74/EC.

7.287 However, the European Communities claims a separate violation of Article 23.1, read together with Article 22.8 and Article 3.7 of the DSU. Under those claims, the European Communities alleges *inter alia* that Canada breached Article 22.8 because it failed to withdraw its suspension of concessions even though the European Communities removed the measure found to be inconsistent with a covered agreement. We also note Canada's argument that it did not breach Article 22.8 of the DSU because the EC implementing measure does not *comply* with the *SPS Agreement*.

7.288 We recall that we considered that the two series of main EC claims were such that they could be addressed independently from each other.[454] Our findings of violation of Article 23.1 and 23.2(a) under the first series of main EC claims are completely unrelated to whether the European Communities implemented the DSB recommendations and rulings in the *EC – Hormones* dispute in substance. Indeed, our findings are based on the failure of Canada to have recourse to the procedures under the DSU as a result of the notification of Directive 2003/74/EC – a purely procedural step. In

[452] Canada's second written submission, paras. 18-44.
[453] EC's first written submission, para. 22.
[454] See paras. 7.162-7.164 above.

contrast, we note that the second series of main EC claims – and the alternative claim of "direct" violation of Article 22.8 of the DSU for that matter – are not premised on the mere existence of an EC implementing measure, but on its *conformity* (presumed or actual) with the *SPS Agreement*.

7.289 Under those circumstances, one cannot exclude that no violation of Article 23.1 of the DSU may be found under the second series of main EC claims even though a violation of Article 23.1 was found under the first series of main EC claims, if only because they are based on different premises.

7.290 We recall in this regard that Article 11 of the DSU instructs us to assist the DSB in discharging its responsibilities and provides that, accordingly, a panel should make an objective assessment of the matter before it. In this case, the matter raised by the European Communities contains two separate elements: a series of claims related to the procedural obligations of the responding party and a series of claims premised on the violation by the responding party of Article 22.8 of the DSU due to compliance by the European Communities with its obligations under the WTO Agreement. We should therefore address both series of claims.

7.291 In addition, we also note that, since our report may be appealed and the Appellate Body can only rule on issues of law, we must provide sufficient factual basis to allow the Appellate Body to complete the analysis, if necessary.[455] In that context, in order to ensure in all instances a positive resolution of this dispute, we consider that proceeding with a review of the second series of main claims raised by the European Communities is appropriate.

7.292 Before proceeding with the review of this second series of claims, we want to stress that in reviewing the EC claims of violation of Article 23.1 read together with Article 22.8 and Article 3.7 of the DSU, our intention is not to substitute ourselves for a compliance panel under Article 21.5 of the DSU. We will make findings with respect to the second series of main claims of the European Communities with the only purpose to reach a conclusion on the violation of the provisions referred to in those claims.

(b) Order of review of the second series of main claims by the European Communities

7.293 We recall that the second series of EC claims is that Canada breaches Article 23.1, read together with Articles 22.8 and 3.7 of the DSU. We also note that the European Communities argues more particularly that Article 22.8 prohibits the continued unilateral application of the suspension of concessions or other obligations when the measure which has been found inconsistent is removed. We conclude from this that the EC claim under Article 23.1 is conditioned by the EC claim under Article 22.8 or, more precisely, that the findings that the European Communities wants us to make in relation to Article 23.1 are dependent on the findings that the European Communities wants us to make under Article 22.8. In other words, the second series of claims of the European Communities is premised on a violation by Canada of its obligations under Article 22.8.

7.294 We therefore conclude that we should begin our analysis of the second series of main claims of the European Communities with a review of the compatibility of Canada's measure at issue with Article 22.8 of the DSU. We consider that:

(a) if we find a breach of Article 22.8 of the DSU, we will proceed with reviewing the EC claims of violation of Articles 23.1 and 3.7 of the DSU, read together with Article 22.8;

[455] See, e.g., Appellate Body Reports on *Canada – Periodicals*, DSR 1997:I, p. 449 at 469; *Australia – Salmon*, para. 118; and *Korea – Dairy*, para. 92.

(b) if we find no violation of Article 22.8, there will be no need for us to proceed any further with the review of these second series of claims by the European Communities.

7.295 We now proceed with our review of the EC claim under Article 22.8 of the DSU.

3. Violation of Article 22.8 of the DSU

(a) Preliminary remarks

7.296 Article 22.8 reads as follows:

> "The suspension of concessions or other obligations shall be temporary and shall only be applied until such time as the measure found to be inconsistent with a covered agreement has been removed, or the Member that must implement recommendations or rulings provides a solution to the nullification or impairment of benefits, or a mutually satisfactory solution is reached. In accordance with paragraph 6 of Article 21, the DSB shall continue to keep under surveillance the implementation of adopted recommendations or rulings, including those cases where compensation has been provided or concessions or other obligations have been suspended but the recommendations to bring a measure into conformity with the covered agreements have not been implemented."

7.297 In light of terms of Article 22.8 and the arguments of the parties, we believe that two preliminary questions have to be addressed with respect to the violation of Article 22.8:

(a) one is when the suspension of concessions should cease to be applied;

(b) another one is what is meant by "the measure found to be inconsistent with a covered agreement".

7.298 Regarding the first question, we recall that the terms of Article 22.8 make it clear that countermeasures may remain in place only until such time as the measure found to be inconsistent by the DSB is removed. In other words, the removal of the illegal measure by the losing party must lead, without delay, to the removal of the suspension of obligations by the Member authorized by the DSB to suspend concessions.

7.299 Regarding what is meant by "the measure found to be inconsistent with a covered agreement", one interpretation could be to consider that the measure found to be inconsistent was Directive 96/22/EC.[456] This measure was removed. However, such an interpretation is unsatisfactory, as Directive 96/22/EC was replaced by Directive 2003/74/EC which also imposes an import ban. The Panel notes that the European Communities agrees that the phrase "until such time as the measure found to be inconsistent with a covered agreement has been removed" means that the illegality itself, and not only the measure, has been removed.[457]

7.300 The Panel believes that the term "measure" should not be interpreted narrowly as applying only to the legislation at issue. What Canada challenged as a complainant in the *EC – Hormones* case was an import restriction on meat and products from cattle treated with growth promoting hormones. We consider that this interpretation is confirmed by the second sentence of Article 22.8 which refers

[456] Official Journal of the European Communities, No. L 125, 23 May 1996, p. 3.

[457] See EC's first written submission, para. 79, EC's replies to Panel questions after the first substantive meeting, question 55, Annex B-1.

to the DSB keeping under surveillance situations where obligations have been suspended "but the recommendations to bring a measure into conformity with the covered agreements have not been implemented". We read this phrase as implying that what is to be achieved is not the removal of the measure but the actual compliance with the recommendations or rulings of the DSB.

7.301 We therefore conclude that Article 22.8 may be breached only if the European Communities has complied with the recommendations and rulings of the DSB and Canada has failed to immediately remove its suspension of concessions or other obligations.

7.302 We recall that the European Communities considers that this case is *not* about its compliance with the recommendations and rulings of the DSB in the *EC – Hormones* case. We nonetheless note that the European Communities requests us to make findings in relation to Article 22.8 under its main claim and that it did not exclude the possibility for the Panel to review the substance of the EC implementation measure in the context of its conditional allegation of "direct" violation of Article 22.8. We note, however, that such claim was made "in the alternative", i.e. if the Panel found no violation of the DSU under the other EC claims. In the context of its second series of main claims, the European Communities alleges that it does not have to demonstrate that it has complied with the recommendations and rulings of the DSB since it should benefit from a presumption of good faith compliance with respect to Directive 2003/74/EC. We note that Canada argues that the European Communities has not removed the measure found to be inconsistent with a covered agreement. More particularly, Canada argues that the EC implementing measure breaches the *SPS Agreement*.

7.303 Having regard to the arguments of the parties regarding the conformity of the EC implementing measure with the *SPS Agreement*, the Panel believes that it must determine the scope of its jurisdiction in this respect.

(b) Jurisdiction of the Panel

(i) Introduction

7.304 This case is not the first one about compliance of a Member with its obligations under the DSU and, in particular, under Article 23.[458] However, because of the claim raised by the European Communities under Article 22.8 of the DSU, the arguments of Canada and the links between this case and the *EC – Hormones* case – in particular through the question of the compliance of the EC implementing measure with the *SPS Agreement* – the second series of main claims by the European Communities raises a number of questions which, to our knowledge, were never directly addressed before by a panel established under Article 6 of the DSU.

7.305 In support of its claim under Article 23.1 read together with Article 22.8 and Article 3.7 of the DSU, the European Communities alleges in substance that it does not have to demonstrate that its implementing measure is compatible with the *SPS Agreement*. Rather, the European Communities argues that it should be presumed to have removed in good faith the measure found inconsistent with the *SPS Agreement* in the *EC – Hormones* dispute and that this presumption could only be rebutted through a recourse to Article 21.5 of the DSU by the responding party.

7.306 Canada disagrees that the European Communities benefit from any presumption of compliance and argues, on the contrary, that the European Communities failed to demonstrate that it has complied with the *SPS Agreement*.

[458] In *US – Section 301 Trade Act*, Article 23.2(a) and (c) of the DSU were at issue, in *US – Certain EC Products*, Articles 23.1 and 23.2(c) as well as 23.2(a) of the DSU were addressed by the panel and the Appellate Body.

7.307 Therefore, before we proceed any further, we believe that we should answer the two following questions:

(a) In light of the EC claim that it benefits from a presumption of good faith compliance, do we need to determine whether the EC implementing measure *actually* complies with the *SPS Agreement* in order to address the EC claim of violation of Article 23.1 read together with Article 22.8 and Article 3.7 of the DSU?

(b) if yes, do we have the jurisdiction to address the conformity of the EC implementing measure with the *SPS Agreement*?

(ii) Does the Panel need to determine whether the EC implementing measure actually complies with the SPS Agreement in order to address the EC claim of violation of Article 23.1 read together with Article 22.8 and Article 3.7 of the DSU?

Introductory remarks

7.308 Having regard to the arguments of the parties, the Panel considers that it needs to determine:

(a) whether the European Communities can invoke a presumption of good faith compliance; and, if yes,

(b) whether, and how, such a presumption could be rebutted.

7.309 The Panel notes that, generally, when good faith is referred to in a dispute, this is in relation to the measure adopted by the defending party[459], not with respect to a measure adopted by the complaining party – in this case the European Communities. Normally, a complainant does not have to show that it applies a measure in good faith, since this is normally not the measure at issue in the dispute. However, the demonstration by the European Communities of a violation of Article 22.8 by Canada in this case implies that it prove that it has removed the measure found to be inconsistent with a covered agreement in the *EC – Hormones* case. The Panel also recalls that it found above that Canada should have had recourse to the DSU in relation to the EC implementing measure. If Canada had had recourse to the dispute settlement procedures under the DSU – including the procedure provided in Article 21.5 – the European Communities would have been the defending party and its implementing measure would have benefited from a presumption of compatibility with WTO rules.[460] For these reasons, the Panel deems it appropriate not to take position on whether good faith can be invoked only by the defendant. Instead, it will address the issue by disregarding the status of the European Communities as complaining party in this case.

Applicability of the principle of good faith in the WTO and under the DSU

Introduction

7.310 We note that what the European Communities claims in this respect is the existence of a presumption of good faith compliance based on the international law principle of good faith. We note I n this regard that Article 31.3(c) of the Vienna Convention on the Law of Treaties (1969) provides that:

[459] See, e.g., Appellate Body Report on *US – Carbon Steel*, para. 157.

[460] See, e.g., Appellate Body Report on *Canada – Dairy (Article 21.5 – New Zealand and US II)*, para. 66.

> "[t]here shall be taken into account, together with the context: ... (c) any relevant rule of international law applicable to the relations between the parties."

7.311 Having regard to the overarching nature of the principle of good faith in international legal relations, we deem it appropriate to determine first whether there is any basis in public international law for the principle to which the European Communities refers. If this is the case, we will then proceed with determining whether the WTO Agreement in general and the DSU in particular exclude the application of this principle.

General international law

7.312 We note that what the European Communities refers to in its submissions is a presumption that it acted in good faith and thus must be presumed to have complied with the recommendations and rulings of the DSB.

7.313 We are of the view that the principle of good faith could be analysed mainly in respect of the following categories:

(a) good faith conduct in a dispute settlement procedure;

(b) substantive good faith, i.e. with respect to the substantive obligations of a State;

(c) good faith in the interpretation process (Article 31 of the Vienna Convention on the Law of Treaties).

7.314 What the European Communities invokes in this case seems to fall primarily within the category of substantive good faith.

7.315 This allegation of the European Communities raises, in our opinion, two related but distinct issues under general international law:

(a) the first one is whether a presumption that States act in good faith exists under general international law;

(b) the second one is whether such presumption of good faith can be assimilated to a presumption of compliance.

7.316 Good faith is one of the basic principles regarding the creation and execution of legal obligations in public international law.[461] This principle is expressed *inter alia* in Article 26 of the Vienna Convention on the Law of Treaties:

> "Every treaty in force is binding upon the parties to it and must be performed by them in good faith."

7.317 It is implicit from the duty to perform treaty obligations in good faith that a party to an international agreement should be deemed to have acted in good faith in the performance of its treaty obligations. More generally, even though Article 26 provides for an obligation and not a presumption, *pacta sunt servanda* is but only one expression of the principle of good faith. Good faith is a general principle of international law that governs all reciprocal actions of States.[462] We are therefore inclined

[461] See, e.g., ICJ, *Nuclear Tests Case*, Judgement of 20 December 1974, ICJ Reports 1974, p. 473, para. 49.

[462] See also UN Charter, Article 2.2; ICJ, *Corfu Channel Case*, Judgement of 9 April 1949, dissenting opinion by Judge ad hoc B. Ečer, ICJ Reports 1949, p. 119; Malcom N. Shaw: International Law (5th edition),

to agree with the European Communities that every party to an international agreement must be presumed to be performing its obligation under that agreement in good faith.

7.318 Having concluded that, under general international law, States enjoy a presumption of good faith, we now proceed to determine whether presumption of good faith can be equated with presumption of compliance with treaty obligations.

7.319 The Panel notes in this respect that good faith has been defined as a:

> "disposition d'esprit de loyauté et d'honnêteté consistant en ce qu'un sujet de droit ne tente pas de minorer ses obligations, quels qu'en soit l'origine et le fondement ..."[463]

7.320 According to this definition, a State acting in good faith should be honestly seeking to comply with its obligations. A presumption of good faith could thus extend to compliance. It is the understanding of the Panel that States benefit in their actions from the principle that a breach of the principle of good faith cannot be presumed and that any State alleging an abuse of right (*abus de droit*) or, more particularly, a breach of the principle of good faith, must prove it.[464]

7.321 As a result, we note that, under general international law, the European Communities would be entitled to claim a presumption of good faith compliance.

7.322 However, that does not mean that the State invoking good faith compliance, while acting in total good faith, actually complied with its treaty obligations. It could make an illegal interpretation of its obligations without breaching the principle of good faith. Thus, if good faith compliance is presumed, it cannot be a non-rebuttable or *juris et de jure* presumption.

7.323 An additional element to consider is that, under general public international law, *every* State benefits from the application of the principle of good faith. We therefore agree with Canada that if the European Communities can claim good faith compliance, Canada too should also benefit from the same presumption. Unlike in "normal" cases where only the measure adopted by one Member is at issue, in this case the legality of Canada's measure challenged by the European Communities depends on whether the measure taken by the European Communities to comply with DSB recommendations and rulings is WTO consistent. In other words, both parties can invoke the presumption of good faith. However, we do not see the fact that both parties can invoke good faith in relation to diametrically opposed positions as affecting the applicability of this principle in this case. Indeed, we are only dealing with presumptions, not with evidence. As long as these presumptions can be rebutted before a panel, we see no inherent problem to the fact that both parties claim good faith.

The text of the DSU

7.324 The Panel first notes that, with the exception of Articles 3.10 and 4.3, there is no reference to good faith in the DSU. Of those two references, that in Article 4.3 relates specifically to

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p. 811-812: "[Pacta sunt servanda] underlies every international agreement for, in the absence of a certain minimum belief that States will perform their treaties obligations in good faith, there is no reasons for countries to enter into such obligations with each other."

[463] Jean Salmon: *Dictionnaire de droit international public*, p. 134. Black Law Dictionary, 6th ed., para. 693:

> "In common usage the term is ordinarily used to describe that state of mind denoting honesty of purpose, freedom from intention to defraud and, generally speaking, means being faithful to one's duty or obligation."

[464] PCIJ, *Upper Silesia Case*, Judgement of 25 May 1926, Series A. No. 7, p. 30.

consultations. Only that in Article 3, entitled "General Provisions", could have a relevance in this case. However, Article 3.10 reads as follows:

> "It is understood that requests for conciliation and the use of the dispute settlement procedures should not be intended or considered as contentious acts and that, if a dispute arises, all Members will engage in these procedures in good faith in an effort to resolve the dispute. It is also understood that complaints and counter-complaints in regard to distinct matters should not be linked."

7.325 The Panel understands the reference to good faith in Article 3.10 of the DSU to relate to the manner in which parties to a dispute should participate in the dispute (i.e. procedural good faith, as described above), not specifically to whether Members should be presumed to be acting in good faith. Indeed, the reference to good faith is made in relation to "engage[ing] in [DSU] procedures in good faith *in an effort to resolve the dispute*" (emphasis added) and the preceding phrase provides that DSU procedures "should not be intended or considered as contentious acts".

7.326 The Panel therefore considers that Article 3.10 is of limited direct relevance to determine whether the European Communities should benefit from a presumption of good faith compliance under the DSU.

7.327 However, the references to good faith in the DSU are evidence that the DSU does not exclude the application of the principle of good faith in the resolution of disputes. The Panel is of the view that, since the application of the principle of good faith is not expressly excluded by the DSU, it is applicable to WTO Members.[465]

The panel and Appellate Body practice

Presumption and burden of proof

7.328 The Panel notes that, in *US – Wool Shirts and Blouses*, the Appellate Body recalled that:

> "[W]e find it difficult, indeed, to see how any system of judicial settlement could work if it incorporated the proposition that the mere assertion of a claim might amount to proof."[466]

7.329 However, the Appellate Body also mentioned in *Japan – Apples* that:

> "[T]he Appellate Body statement in *EC – Hormones* does not imply that the complaining party is responsible for providing proof of all facts raised in relation to the issue of determining whether a measure is consistent with a given provision of a covered agreement. In other words, although the complaining party bears the burden

[465] The Panel is not of the view that the fact that some covered agreements, such as the *SPS Agreement* (see Article 2.4) expressly provide that measures of a Member which conform to a given agreement shall be presumed to be in accordance with the obligations of that Member under another covered agreement would imply that the presumption of good faith does not apply in the WTO Agreements unless expressly referred to. The Panel considers that the reference to presumption in Article 2.4 of the *SPS Agreement* is to a legal presumption and is intended to address potentially conflicting interpretations between two provisions. The reference in Article 3.2 of the *SPS Agreement* can be explained by the fact that the "international standards, guidelines or recommendations" are not part of the WTO Agreement.

[466] Appellate Body Report on *US – Wool Shirts and Blouses*, DSR 1997:I, p. 323 at 335.

> of proving its case, the responding party must prove the case it seeks to make in response."[467]

7.330 We believe that, in arguing that it enjoys a presumption of good faith compliance, the European Communities is not merely *asserting* its claim of violation of Articles 23.1, 22.8 and 3.7. The EC allegation of existence of a presumption of good faith compliance is only one part – although an essential one – of the EC argumentation supporting its claims. Moreover, the European Communities is not directly asserting that it has complied in relation to the conformity of Canada's measure with Article 22.8, but that it enjoys, as a matter of principle, a presumption that it complied in good faith with its own obligations.

7.331 On its part, Canada argues as a defence that the European Communities did not comply with the recommendations and rulings of the DSB. One may argue that the parties' respective burdens are unbalanced because the European Communities, if one agrees with its position, does not have to make any particular effort to demonstrate prima facie that it has complied with the recommendations and rulings of the DSB. However, it should first be recalled that what is at issue in this case is not directly whether the European Communities has complied with the recommendations and rulings of the DSB, but whether Canada complied with its obligations under Articles 23.1, 22.8 and 3.7 of the DSU. By taking this route, the European Communities takes the risk that its claims may be rejected if the Panel disagrees with the existence of a presumption of good faith compliance.

7.332 We therefore conclude that by invoking a presumption of good faith compliance, the European Communities is not merely asserting its claims under Article 22.8, but rather supporting its claims which are, in essence, claims of violations by Canada, not claims of compliance by the European Communities.

7.333 We therefore find that the European Communities' reliance on a presumption does not amount in this case to merely asserting a claim.

Presumption of good faith

7.334 The Panel notes that the Appellate Body has, on several occasions, recalled that the principle of good faith applies to WTO Members in their relations under the WTO Agreement. The Panel recalls that, in *US – FSC*, the Appellate Body stated that:

> "This pervasive principle [of good faith] requires both complaining and responding Members to comply with the requirements of the DSU (and related requirements in other covered agreements) in good faith." (emphasis added)[468]

7.335 Furthermore, it seems that the Appellate Body understands the obligation to comply with the requirements of the DSU in good faith as implying that Members are to be presumed to act in good faith. In *EC – Tube or Pipe Fittings*, the Appellate Body found that:

> "This excerpt demonstrates that the Panel took into account the European Communities' responses to its questions before reaching its finding. It also indicates that the Panel did not rely exclusively on the presumption of good faith, as Brazil suggests, given that some of the Panel's questions were directed at the *validity* of Exhibit EC-12. If the Panel had placed total reliance on the presumption of good faith, it would have simply accepted the European Communities' assertion that Exhibit EC-12 formed part of the record of the investigation and would not have

[467] Appellate Body Report on *Japan – Apples*, para. 154.
[468] Appellate Body Report on *US – FSC*, para. 166.

> posed questions to assess the consistency of Exhibit EC-12 with other evidence contained in the record. Therefore, we are satisfied that the Panel "took steps to assure [itself] of the validity of [Exhibit EC-12] and of the fact that it forms part of the contemporaneous written record of the EC investigation." (footnotes omitted – emphasis added)[469]

7.336 As mentioned above, there is no express exclusion of the application of the principle of good faith in the DSU or in the WTO Agreement. As noted by the panel on *Korea – Procurement*:

> "Article 3.2 of the DSU requires that we seek within the context of a particular dispute to clarify the existing provisions of the WTO agreements in accordance with customary rules of interpretation of public international law. However, the relationship of the WTO Agreements to customary international law is broader than this. Customary international law applies generally to the economic relations between the WTO Members. Such international law applies to the extent that the WTO agreements do not 'contract out' from it. To put it another way, to the extent there is no conflict or inconsistency, or an expression in a covered WTO agreement that implies differently, we are of the view that the customary rules of international law apply to the WTO treaties and to the process of treaty formation under the WTO."[470]

7.337 More precisely, in *US – Section 211 Appropriations Act*, the Appellate Body recalled that:

> "... where discretionary authority is vested in the executive branch of a WTO Member, it cannot be assumed that the WTO Member will fail to implement its obligations under the *WTO Agreement* in good faith. Relying on these rulings, and interpreting them correctly, the Panel concluded that it could not assume that OFAC would exercise its discretionary executive authority inconsistently with the obligations of the United States under the *WTO Agreement*. Here, too, we agree." (emphasis added)[471]

7.338 The parties have argued on the relevance of the report in *EC – Bananas III (Article 21.5 – EC)*. The European Communities notes that this report was never adopted by the DSB. We nevertheless recall that the Appellate Body, in *Japan – Alcoholic Beverages II*, found that panels may seek guidance from unadopted panel reports. In *EC – Bananas III (Article 21.5 – EC)*, the panel rejected the EC assertion of a presumption of consistency. In that case, the European Communities requested the panel to find that its implementing measures "must be presumed to conform to WTO rules unless their conformity has been duly challenged under the appropriate DSU procedures". This position seems largely similar to the position adopted by the European Communities in the present case, where it claims that Canada will breach Article 23 even if it rebuts the presumption of compliance because it failed to use the right forum to contest it (i.e. Article 21.5 of the DSU).

7.339 The panel in *EC – Bananas III (Article 21.5 – EC)*, agreed with the European Communities that there was normally no presumption of inconsistency attached to a Member's measures in the WTO dispute settlement system. This was subsequently confirmed by the Appellate Body in *Chile – Alcoholic Beverages*[472] and it is now well established that no presumption of bad faith can be applied to a Member's measure. However, the panel in *EC – Bananas III (Article 21.5 – EC)* considered that

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[469] Appellate Body Report on *EC – Tube or Pipe Fittings*, para. 127.
[470] Panel Report on *Korea – Procurement*, para. 7.96.
[471] Appellate Body Report on *US – Section 211 Appropriations Act*, para. 259 (original footnote omitted).
[472] Appellate Body Report on *Chile – Alcoholic Beverages*, para. 74.

the failure, as of a given point in time, of one Member to challenge another Member's measures could not be interpreted to create a presumption that the first Member accepts the measures of the other Member as consistent with the WTO Agreement.[473]

7.340 First, we find the above reasoning of the Panel in *EC – Bananas III (Article 21.5 – EC)* convincing.

7.341 Second, in the present case, however, the European Communities does not actually allege that there is a presumption of acceptance by Canada that the measure is consistent with the WTO Agreement because Canada failed to challenge the measure. The European Communities claims that there is a presumption of compliance based on the presumption of good faith and that this presumption can only be rebutted in the appropriate forum, i.e. by invoking Article 21.5 of the DSU.

7.342 Canada argues that the presumption of good faith compliance cannot supersede the multilateral authorization of the DSB to Canada to suspend concessions.

7.343 As already mentioned, we first note that Article 22.2 and 22.7 of the DSU refers to "authorization" of the DSB. Canada has no obligation under the DSU to apply the sanctions authorized by the DSB.[474] Second, we note that Article 22.8 provides that the suspension of obligations "shall only be applied until such time as the measure found to be inconsistent with a covered agreement has been removed, or the Member that must implement recommendations or rulings provides for a solution to the nullification or impairment of benefits". There is no reference to the DSB in that phrase and nothing in this provision suggests that a Member suspending concessions can continue to do so as long as the authorization of the DSB has not been repealed by the DSB. On the contrary, it seems that it is for the Member concerned to draw the consequences of a removal of the violation. In other words, the removal of the measure found to be inconsistent with a covered agreement supersedes the DSB authorization to suspend concessions.

Is the presumption of good faith compliance rebuttable only in a specific forum?

7.344 We note that the European Communities claims that the presumption of good faith compliance is rebuttable, but only in the appropriate forum, i.e. by the complaining party in the original case taking the initiative of having recourse to a dispute settlement procedure under Article 21.5 of the DSU.[475] The European Communities alleges a "jurisprudential" need for an irrebuttable presumption to fill up a gap in the DSU and allow respondents to exit from post-retaliation situations.

7.345 Canada argues, on the contrary, that an Article 21.5 proceeding is not the only avenue available if there is a disagreement as to the adoption of a compliance measure and that, in any event, it is not open exclusively to Canada, but also to the European Communities.[476]

7.346 It is therefore important for the Panel to determine the extent to which the unavailability of any legal recourse for the European Communities in a post retaliation situation may justify that the presumption of good faith compliance be irrebuttable, except through recourse to the procedure provided in Article 21.5 of the DSU.

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[473] Panel Report on *EC – Bananas III (Article 21.5 – EC)*, para. 4.13.

[474] See, e.g., *Canada – Aircraft Credits and Guarantees* and *Brazil – Aircraft*. In both cases, authorization of suspension of concessions has been granted by the DSB but the complaining party has not applied the authorized sanction.

[475] EC's reply to Panel question 4(b) after the first substantive meeting.

[476] See Canada's reply to Panel questions 36, 37 and 45 after the first substantive meeting, Annex B-2.

7.347 We first note that nowhere does the DSU provide that a presumption of good faith compliance should be rebuttable only through recourse to Article 21.5 of the DSU.

7.348 Second, it appears that, even under the current DSU, several means seem *a priori* to be available to the European Communities to obtain termination of the suspension of concessions or other obligations:

(a) Good offices and consultations;

(b) Article 21.5 of the DSU;

(c) Arbitration under Article 25 of the DSU; and

(d) recourse to a normal panel against the continuation of the retaliations (as in this case).

7.349 The Panel is mindful that the option naturally coming to mind when it comes to reviewing compliance is the procedure provided under Article 21.5 of the DSU. The Panel is aware of the broad language ("such dispute shall be decided through recourse to these dispute settlement procedures") used in Article 21.5 and that such language could be deemed to encompass any procedure available under the DSU for the resolution of disputes. The Panel is, however, of the opinion that other terms in Article 21.5 support the view that the Article 21.5 procedure is actually a panel procedure with a shorter deadline. In this regard, the Panel reads the phrase "including whenever possible resort to the original panel" not as meaning that resort to a panel is generally preferred, but as requesting resort to the panelists that reviewed the original case, rather than to other individuals.

7.350 The Panel also notes that this dispute is evidence that a practicable alternative exists to a recourse to Article 21.5. We recall in this respect that even though the European Communities claims a violation of the DSU by Canada, its claim under Article 22.8 of the DSU is based on the compliance of its implementing measure with the WTO Agreement, whether presumed (as part of the second series of main EC claims under Article 23.1 read together with Article 22.8 and Article 3.7) or demonstrated (as in its alternative "direct" claim of violation of Article 22.8). While Members enjoy complete discretion in the way they bring the measure at issue into conformity with the covered agreements, the findings already made by the Panel with respect to Article 23.2(a) and 23.1 of the DSU and the findings the Panel will make under Article 22.8 will have an impact on whether Canada may maintain, suspend or withdraw the suspension of obligations it currently applies.

7.351 We recall that the European Communities considered that Article 21.5 was not an avenue open to the party claiming compliance, but only to the complainant in the original case.[477] Both parties have discussed the relevance of the only case where a party found in breach of its obligations requested an Article 21.5 panel, i.e. the *EC – Bananas III (Article 21.5 – EC)* panel.

7.352 We note that, in the *EC – Bananas III (Article 21.5 – EC)* case, the panel did not conclude that it could not perform its duties under Article 21.5. The panel, referring to the comments made by Japan as a third party, noted that allowing the defendant before the original panel to initiate a procedure under Article 21.5 presented certain "practical problems or anomalies". The panel was also sympathetic to the concerns of India as a third party that, in an appropriate case, a respondent-initiated Article 21.5 proceeding should be allowed.[478] The Panel concluded:

[477] EC's reply to Panel question 1 after the first substantive meeting, Annex B-1; EC's second written submission, paras. 62-63.

[478] Panel Report on *EC – Bananas III (Article 21.5 – EC)*, para. 4.18.

> "In our view, we would not rule out the possibility of using Article 21.5 in such a manner, particularly when the purpose of such initiation was clearly the examination of the WTO-consistency of implementing measures."[479]

7.353 We are therefore not convinced that Article 21.5 is the only avenue available to address a claim of compliance by a Member alleging to have complied with recommendations and rulings of the DSB. Neither do we believe that proceedings under Article 21.5 are open only to the original complainant.

7.354 For these reasons, the Panel does not agree that the presumption of good faith compliance which the European Communities enjoys should be rebuttable only through a recourse by the complainants in the original case to Article 21.5 of the DSU.

Conclusion

7.355 On the basis of the above:

(a) We note that, under general international law, the corollary to the obligation to perform treaty obligations in good faith is the presumption that Members act in good faith when performing such obligations.

(b) We find that the general principle of good faith and the presumption of good faith performance of a Member's obligations apply in relation to Members' obligations under the WTO Agreements, including the DSU, as interpreted in accordance with customary rules of interpretation of public international law.

(c) We also note that there is no presumption of bad faith under general international law and find that no presumption of bad faith applies under the DSU as interpreted in accordance with customary rules of interpretation of public international law.

(d) We find that the presumption of good faith compliance alleged by the European Communities is at best legally identical to the principle of good faith performance of treaty obligations. We do not find in the DSU as interpreted in accordance with customary rules of interpretation of public international law any ground supporting a specific presumption of compliance for Members having to implement DSB recommendations and rulings.

(e) Moreover, we find no support in the DSU to suggest that this presumption may only apply to the measure taken by the European Communities and not to the measures adopted by Canada.

(f) As a consequence, while we agree with the existence of a presumption of good faith compliance, we do not agree with the European Communities that the presumption of good faith that it enjoys may only be rebutted in an Article 21.5 procedure. We find, on the contrary, that this presumption, because it applies to measures taken by all parties, must be rebuttable before this Panel. Just as the EC allegations are intended to rebut the presumption of good faith conformity of Canada's retaliatory measures with Article 22.8 of the DSU, Canada should be allowed to rebut the presumption of EC compliance by proving actual non-compliance.

[479] Ibid.

7.356 In reaching these conclusions, we do not consider that we add to or diminish the rights and obligations of WTO Members. We do not apply the presumption of good faith compliance independently from the obligations of the European Communities under the WTO Agreement. The European Communities has an obligation to comply with the WTO Agreement in general[480] and with the recommendations and rulings of the DSB and the general principle of good faith implies that the European Communities do so in good faith. In doing so we apply the principle of good faith consistently with WTO law and general public international law.[481]

7.357 We have also found above that we could not agree with the European Communities and base our findings of violation of Article 23.1 read in conjunction with Article 22.8 and 3.7 of the DSU on an irrebuttable presumption of good faith compliance by the European Communities. Whereas the European Communities enjoys a presumption of good faith compliance, this presumption is rebuttable. We agree that, for all practical purposes, this amounts to addressing the EC "alternative" claim of violation of Article 22.8 *per se*. However, this is not the result of us merely disregarding the order in which the European Communities wanted us to review this case. We are still reviewing the EC claim of violation of Article 23.1, read together with Articles 22.8 and 3.7. We are not reviewing a claim of violation of Article 22.8 in isolation.

(iii) Does the Panel have jurisdiction to address the compliance of the EC implementing measure with the SPS Agreement?

7.358 We are mindful that our terms of reference do not include any provision of the *SPS Agreement* referred to by the parties during these proceedings and that "[A] panel cannot assume jurisdiction that it does not have."[482] *Stricto sensu*, the conformity of the EC measure with the provisions of the *SPS Agreement* referred to in this case is not part of our mandate. This means that reviewing alleged violations of the *SPS Agreement* is not part of our mandate either and that we are not expected to make *findings* on those provisions.

7.359 However, this absence of reference to the *SPS Agreement* is understandable since the European Communities is not seeking a finding of violation of the *SPS Agreement* by the responding party.

7.360 Moreover, we note that the European Communities claims in its request for establishment of a panel that Canada breached Article 22.8

> "Canada has acted inconsistently with Article 22.8 of the DSU by failing to apply the suspension of concessions or other obligations only until such time as the measure found to be inconsistent with a covered agreement has been removed, or the implementing Member has provided a solution to the nullification or impairment of benefits previously caused to Canada."[483]

7.361 This statement, which essentially repeats the terms of Article 22.8, must be read in conjunction with other relevant remarks of the European Communities in its request for establishment of a panel. For instance, in the introduction, the European Communities stated that:

> "[t]his request concerns Canada's continued suspension of concessions and other obligations under the covered agreements, without recourse to the procedures

[480] See Article XVI:4 of the WTO Agreement.
[481] As explicitly expressed in Article 2.2 of the Charter of the United Nations, as well as in Article 26 of Vienna Convention on the Law of Treaties.
[482] Appellate Body Report on *India – Patents (US)*, para. 92.
[483] WT/DS321/6.

established by the DSU, after the European Communities has removed the measures found to be inconsistent with WTO law in case DS 48, *European Communities – Measures concerning meat and meat products (Hormones)* ('*EC – Hormones*')."[484]

and subsequently:

"The European Communities subsequently removed the measure found to be inconsistent with a covered agreement. It adopted Directive 2003/74/EC of the European Parliament and of the Council of 22 September 2003 amending Council Directive 96/22/EC concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists. The Directive was published and entered into force on 14 October 2003.

In conformity with the recommendations and rulings of the DSB and the covered agreements, the new EC legislation is based on comprehensive risk assessments, in particular on the opinions of the independent Scientific Committee on Veterinary Measures relating to Public Health. The risk assessments focussed on potential risks to human health from hormone residues in bovine meat and meat products, in particular such risks arising from residues of six hormonal substances: oestradiol-17β, testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate. In carrying out the risk assessments, the European Communities initiated and funded a number of specific scientific studies and research projects. It addressed specific requests to the United States, Canada and third countries to provide any recent scientific data and information in their possession. It took account of the findings of various independent expert bodies.

In light of the risk analyses carried out, the European Communities concluded that the avoidance of intake of oestradiol-17β is of absolute importance to human health and that, consequently, the placing on the market of meat containing this substance should be prohibited. With respect to testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate, and on the basis of the available pertinent scientific information reflected in the above-mentioned risk analyses, the European Communities provisionally prohibited the placing on the market of meat containing these substances because the relevant scientific evidence was insufficient.

On 27 October 2003, the European Communities notified to the DSB the adoption, publication and entry into force of this Directive as well as the preceding scientific risk assessments. In the same communication, the European Communities explained that it considers itself to have fully implemented the recommendations and rulings of the DSB in the *EC – Hormones* dispute and that, as a consequence, it considers Canada's suspension of concessions vis-à-vis the European Communities to be no longer justified.[485]

7.362 In the Panel's view, one instance of violation of Article 22.8 occurs when the suspension is maintained even though the "measure found to be inconsistent ... has been removed". The lengthy explanation above demonstrates that the claims of the European Communities under Article 22.8 are related to its alleged removal of the "measure found to be inconsistent" with the *SPS Agreement*.

7.363 The Panel notes the arguments of the parties in reply to a question on its jurisdiction to review the compatibility of the EC implementing measure with the *SPS Agreement*. Canada replied that the

[484] WT/DS321/6 (emphasis added).
[485] WT/DS321/6 (original footnotes omitted).

Panel has jurisdiction to review the consistency of the European Communities' new measure with Articles 3.3, 5.1 and 5.7 of the *SPS Agreement.* Canada considers that the Panel's determination that the European Communities has actually removed its offending measure is a prerequisite to any finding that Canada has breached Article 22.8 of the DSU by maintaining its suspension of concessions.[486] The European Communities replied that, in light of the Appellate Body practice, the Panel has, in the present case, no jurisdiction to address Articles 3.3, 5.1 and 5.7 of the *SPS Agreement.* The European Communities adds that, at best, one could venture to draw an analogy to affirmative defences.[487]

7.364 We do not consider that an analogy could be drawn between the reference by the parties to provisions of the *SPS Agreement* in this case and the notion of "affirmative defence". In the opinion of the Panel, an affirmative defence would imply that the responding party invoke a provision of a covered agreement as a justification for a breach of another provision. This is not the case here. Canada does not argue the incompatibility of the EC implementing measure as a *justification* for a breach of Article 22.8. Nor does it seem to invoke the incompatibility of the EC implementing measure as a justification for a breach of Article 23. The Panel concludes that any jurisdiction it may have to review the compatibility of the EC implementing measure with the *SPS Agreement* cannot result from the fact that Canada would have invoked the *SPS Agreement*, including as an affirmative defence.

7.365 We also note the argument of the European Communities that:

> "[this] issue is a perfect illustration of the problems arising if an implementing member is forced to bring a case alleging compliance, instead of the original complaining party bringing a case alleging non compliance ... The terms of reference become wholly devoid of their meaning and the panel's jurisdiction turns into a moving target depending on whatever allegations of inconsistency the "defending" parties will come up with. It is clear that the dispute settlement system is not designed to accommodate such a procedural constellation."[488]

7.366 We recall that, as mentioned above, the EC request for establishment of a panel is silent regarding the *SPS Agreement*. We do not agree, however, that the terms of reference of the Panel become wholly devoid of meaning because of the references made by the parties to provisions of the *SPS Agreement.* Neither do we consider that this modifies our terms of reference. We recall that the European Communities claims a violation by Canada of Article 22.8 of the DSU which is premised on the compliance of the EC implementing measure (Directive 2003/74/EC) with the *SPS Agreement*. A discussion of the compatibility of the measure with provisions of the *SPS Agreement* is, thus, the immediate consequence of the inclusion of Article 22.8 of the DSU in the EC request for establishment of a panel. As such, our mandate remains defined by the EC request for establishment of a panel.

7.367 We are mindful that the responding party could bring several allegations of violations with respect to the EC implementing measure. We note however that the European Communities did not exclude the possibility for the Panel to consider the actual compatibility of Directive 2003/74/EC with the *SPS Agreement* as part of its alternative "direct" claim under Article 22.8 of the DSU. Such a review would imply that the Panel address the compatibility of the EC implementing measure with the

[486] Canada's reply to Panel questions after the first substantive meeting, question 65, Annex B-2, para.55.

[487] EC's reply to Panel questions after the first substantive meeting, question 65, Annex B-1, paras. 239-241.

[488] EC's reply to Panel question 65 after the first substantive meeting, Annex B-1, para. 240. See also EC's reply to Panel question 62 after the first substantive meeting, Annex B-1.

SPS Agreement. While the Panel must comply with its terms of reference, nothing in the DSU prevents the Panel from considering the compatibility of the EC implementing measure with the *SPS Agreement* if this is necessary in order to make the findings required by those terms of reference.

7.368 Moreover, we note that, whereas the European Communities "[did] not believe that it [was] necessary for the Panel to look into any scientific issue to make its necessary findings and rulings within its terms of reference in this particular case", the European Communities did not exclude that the Panel could address the scientific issues at stake since it suggested that, in such a case, the consultation of scientific experts would be absolutely necessary.[489] The parties have extensively discussed the question of the compatibility of the EC implementing measure with certain provisions of the *SPS Agreement*, have agreed to the consultation of experts on the scientific issues relating to the compatibility of the measure with the *SPS Agreement* and have extensively commented on these scientific issues.

7.369 We conclude from this that the Panel should be entitled to determine whether the European Communities has removed the measure found to be inconsistent with a covered agreement in order to establish whether Article 22.8 has been breached by Canada. Indeed, the Panel considers that, since the European Communities made a claim of violation of Article 22.8, the compatibility of its implementing measure becomes *ipso facto* an issue that the Panel will have to address if it reviews any of the EC claim relating to Article 22.8. The fact that the European Communities alleges that it benefits from a presumption of good faith compliance does not affect this conclusion. Under both of its Article 22.8 claims, the European Communities needs to demonstrate that it has removed the measure found to be inconsistent. The presumption of good faith compliance does not affect what needs to be demonstrated. It simply shifts the burden of proof since, in application of the presumption of good faith compliance, the European Communities has, in this dispute, made a prima facie case of violation of Article 22.8 which Canada has to rebut.

7.370 The Panel notes that, pursuant to its mandate, it is only expected to make findings of violation in relation to Article 22.8 of the DSU, the breach of which is alleged by the complaining party. The Panel nonetheless recalls that, for the reasons mentioned above and irrespective of which one of the two Article 22.8 claims is addressed, it will have to determine whether the European Communities has removed the measure found to be inconsistent. Since what has to be demonstrated is a consistency or inconsistency with provisions of the *SPS Agreement*, this is not really an issue of fact but a legal question, which adds to the complexity of the situation before the Panel.

7.371 The Panel is fully conscious of the challenges attached to assessing whether the EC implementing measure is not inconsistent with the provisions of the *SPS Agreement* referred to by the parties in this case. The Panel also notes that, in a case like this one, it is largely dependent on the responding party, not on the complainant, as far as allegations of incompatibility of the EC implementing measure are concerned. However, we believe that it is in the interest of the responding party to demonstrate the incompatibility of the implementing measure. We can count on its full cooperation in this respect, and we have experienced it in this case. The Panel also agrees that, since the allegations of violation of the *SPS Agreement* were not exhaustively listed in its terms of reference and depended on the parties raising them in the course of the procedure, this could have made it difficult to circumscribe the scope of its review under the *SPS Agreement*. We note, however, that in this particular case the legal arguments regarding the conformity of the EC implementing measure with the *SPS Agreement* were all raised early in the proceedings and that no party complained that it had not been given sufficient opportunity to comment on the other party's legal arguments.

[489] EC's reply to Panel question 74 after the first substantive meeting, Annex B, para, 275. The Panel notes that the European Communities raised an alternative claim of violation of Article 22.8 of the DSU and Articles I and II of the GATT 1994, based on its alleged actual compliance with the recommendations and rulings of the DSB in the *EC – Hormones* case

7.372 We therefore conclude that we should address the compatibility of the EC implementing measure with the provisions of the *SPS Agreement* referred to by the parties to the extent necessary to determine, with respect to the EC claim relating to Article 22.8, whether the EC "measure found to be inconsistent" in the *EC – Hormones* case has been removed. We are mindful of the procedural problems raised by this approach, but we do not consider that, by proceeding in this manner, we are exceeding our jurisdiction to the extent that such a review is necessary in order to address the EC claims under Article 22.8 of the DSU.

7.373 The Panel notes in this respect that it is not the first time that a dispute settlement entity, when confronted with a procedurally a-typical issue, decided to adopt a pragmatic solution and perform functions similar to those of an Article 21.5 panel. In the Article 22.6 arbitration in the *EC – Bananas III* case the arbitrator decided to adopt the most "logical way forward":

> "4.10 ... the European Communities argues that we should not consider the consistency of its new banana regime. First, it argues that to do so would go beyond our terms of reference, which it suggests are limited to determining the level of suspension and its equivalence to the level of nullification or impairment. As noted above, however, setting the level of nullification or impairment may require consideration of whether there is nullification or impairment flowing from a WTO-inconsistency of the new banana regime."

7.374 We too believe that our approach to consider, to the extent necessary, the compatibility of the EC implementing measure with the *SPS Agreement* is the most logical way forward under the circumstances, having regard to our duty to assist the parties and the DSB in solving this dispute and, in particular, to determine whether, as claimed by the European Communities, there is a violation of Article 23.1 in conjunction with Article 22.8 and Article 3.7 of the DSU. This is consistent with our duty to make an objective assessment of the matter before us pursuant to Article 11 of the DSU.[490]

7.375 We also note that panels have not hesitated in the past to consider other provisions than those on which findings had been requested as part of the context of those provisions.[491]

7.376 Therefore, the Panel believes that these are sufficient reasons for it to conclude that it has jurisdiction to consider the compatibility of the EC implementing measure with the *SPS Agreement* as part of its review of the claim raised by the European Communities with respect to Article 22.8 of the DSU.

(c) Burden of proof

7.377 We note that the European Communities considers that it has made a prima facie case of violation of the DSU provisions, and that, since it cannot be requested to prove a negative, it is for Canada to prove a violation of the *SPS Agreement* by the EC implementing measure. The European Communities also argues that it enjoys a presumption of good faith compliance with the recommendations and rulings of the DSB in the *EC – Hormones* dispute.[492] Canada considers that this dispute does not concern an EC measure taken as part of its regular day-to-day business of governing, prior to the engagement of the WTO dispute settlement mechanism. Nor does it concern a measure that the EC has taken to comply within the reasonable period of time, and prior to the adoption of DSB authorization to suspend concessions. Any measure taken by the European Communities in either of these scenarios would be presumed to comply with its international obligations unless otherwise challenged. Rather, the dispute before this Panel concerns the failure of

[490] See Section VII.C.2.(a) above.
[491] Panel Report on *India – Quantitative Restrictions*, para. 5.26.
[492] EC's first written submission, paras. 90-92.

the European Communities to correct, within the reasonable period of time, a measure that had been found by the DSB to be inconsistent with the WTO obligations of the European Communities, and as a result the DSB authorized Canada to suspend concessions. For Canada, the existence of the authorization by the DSB of Canada's measure distinguishes this case from those situations in which a general presumption of compliance would apply to the EC measure.

7.378 The principles regarding allocation of burden of proof have been well established since the early days of the WTO dispute settlement system and the Panel did not deem it necessary to repeat them in relation to the other claims of the European Communities. However, having regard to the importance given by the parties to the question of burden of proof in relation to the compatibility of the EC measure with the *SPS Agreement*, the Panel considers that it needs to clarify how it addressed burden of proof in relation to the EC claim under Article 22.8.

7.379 First, we deem it necessary to recall that, in *US – Wool Shirts and Blouses*, the Appellate Body stated that:

> "... various international tribunals, including the International Court of Justice, have generally and consistently accepted and applied the rule that the party who asserts a fact, whether the claimant or the respondent, is responsible for providing proof thereof. Also, it is a generally-accepted canon of evidence in civil law, common law and, in fact, most jurisdictions, that the burden of proof rests upon the party, whether complaining or defending, who asserts the affirmative of a particular claim or defence."[493]

7.380 With respect to the violation of Article 22.8 as such, the Panel considered that it had, in principle, no reason to address burden of proof any differently than any other panel established under Article 6 of the DSU. Indeed, as stated by the Complainant itself, this case is about a measure taken by Canada. The Panel does not agree with Canada that the fact that this dispute takes place in the context of the EC alleged late compliance with the recommendations and rulings of the DSB in the *EC – Hormones* dispute should have any impact on the question of the burden of proof regarding the actual *claim* before us. This means that the principles identified by the Appellate Body above apply, and that the European Communities must prove its claim that Canada breaches Article 22.8 of the DSU.

7.381 Yet, one of the particularities of this case is that the European Communities claim of violation of Article 22.8 of the DSU by Canada is premised on the removal of the EC measure found to be inconsistent with the *SPS Agreement*. In other words, in order to demonstrate that Canada has breached Article 22.8, the European Communities also alleges that its implementing measure is itself in conformity with the *SPS Agreement*.

7.382 In theory, this should not raise any difficulty in terms of burden of proof since it is well established that each party has to prove its own allegations. We agree, however, with the European Communities that in a case like this one, this could generate for the complainant at the beginning of the proceedings a situation equivalent to having to "prove a negative", since the spectrum of provisions against which the legality of the EC measure may have to be reviewed remains very broad as long as the respondent has not made its own allegations of inconsistency of the implementing measure. However, we recall that we found above that the European Communities enjoyed a presumption of good faith compliance, even though that presumption was rebuttable before this Panel. As soon as the European Communities established a prima facie case[494] thanks to the presumption of

[493] Appellate Body Report on *US – Wool Shirts and Blouses*, p. 14. See also Appellate Body Report on *Canada – Dairy (Article 21.5 – New Zealand and US II)*, para. 66.

[494] See Appellate Body Report on *EC – Hormones*, para. 98.

good faith compliance, the burden shifted to Canada to rebut that presumption. We recall that "... a prima facie case is one which, in the absence of effective refutation by the defending party, requires a panel, as a matter of law, to rule in favour of the complaining party presenting the prima facie case."[495] We believe that Canada sufficiently refuted the EC allegation of compliance in its first written submission through positive evidence of breach of the *SPS Agreement* by the European Communities. In its subsequent submissions before the Panel, the European Communities responded to the allegations of violation made by Canada. Thus, the European Communities never actually had to "prove a negative" in this case.

7.383 While the presumptions based on good faith enjoyed by each party may have played a role in the burden of proof in the early stage of the Panel proceedings, it is the opinion of the Panel that they eventually "neutralized" each other since each party also submitted evidence in support of its allegations. Ultimately, each party had to prove its specific allegations in response to the evidence submitted by the other party.[496] Thereafter, when considering whether an allegation had been proven or not, the Panel followed the practice of other panels to weigh all the evidence before it.

(d) Compatibility of the EC implementing measure with the provisions of the *SPS Agreement*

(i) The EC implementing measure

7.384 As already noted, the European Communities has had a ban on the placing on the market, including a ban on the importation, of beef treated with certain hormones for growth promotion purposes since 1988. The hormones concerned are oestradiol-17β, testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate. We note that the European Communities stated in its first submission that the DSB recommendations in the *EC – Hormones* cases had been implemented through the adoption, on 22 September 2003, of Directive 2003/74/EC the transposition deadline of which was 14 October 2004.

7.385 The European Communities claims that the Directive is based on a risk assessment the results of which "sufficiently warrant" the definitive import prohibition on meat and meat products treated with oestradiol-17β and "provide the available pertinent information" on the basis of which the provisional prohibition regarding the other five hormones has been enacted.

7.386 The Panel understands that, according to the European Communities, its risk assessment:

(a) is composed of three opinions issued by the EC Scientific Committee on Veterinary measures relating to Public Health (SCVPH) in 1999, 2000 and 2002, the 2000 and 2002 Opinions constituting reviews of the 1999 Opinion;

(b) is supported by the 17 studies initiated and funded by the European Communities between 1998 and 2001 in order to obtain as much as possible of the missing scientific information that was identified by the panel and the Appellate Body in the *EC – Hormones* case.

7.387 Specifically, the European Communities argues that the 17 scientific studies it commissioned resulted in numerous publications which, along with the pre-existing scientific data, were examined by the SCVPH. The SCVPH issued its first opinion entitled "Assessment of Potential Risks To Human Health From Hormone Residues in Bovine Meat And Meat Products" on 30 April 1999 (hereafter the "1999 Opinion").

[495] Appellate Body Report on *EC – Hormones*, para. 104.
[496] See Appellate Body Report on *Japan – Apples*, para. 154.

7.388 The 1999 Opinion contained the following major conclusions:

(a) As concerns excess intake of hormone residues and their metabolites, and in view of the intrinsic properties of hormones and epidemiological findings, a risk to the consumer had been identified with different levels of conclusive evidence for the six hormones in question.

(b) In the case of oestradiol-17β, there was a substantial body of recent evidence suggesting that it had to be considered as a complete carcinogen, as it exerted both tumour initiating and tumour promoting effects. The data available did not, however, allow a quantitative estimate of the risk.

(c) For the other five hormones at issue, in spite of the individual toxicological and epidemiological data described in the report, the current state of knowledge did not allow a quantitative estimate of the risk.

(d) For all six hormones endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects could be envisaged. Of the various susceptible risk groups, prepubertal children was the group of greatest concern. Again the available data did not enable a quantitative estimate of the risk.

(e) In view of the intrinsic properties of the hormones and in consideration of epidemiological findings, no threshold levels could be defined for any of the six substances.[497]

7.389 In 2000, the SCVPH reviewed two reports, one from the Committee on Veterinary Medicinal Products and one from the UK Veterinary Products Committee, to determine whether the science contained within warranted altering the findings and conclusions of the 1999 Opinion. In May 2000, the SCVPH concluded the following:

> "The reports of the UK's Veterinary Products Committee subgroup and of the Committee on Veterinary Medicinal Products presented for review to the Scientific Committee, as well as recent scientific information, did not provide convincing data and arguments demanding revision of the conclusions drawn in the opinion of the SCVPH of April 30th, 1999, on the potential risks to human health from hormone residues in bovine meat and meat products.
>
> The SCVPH discussed again the obvious gaps in the present knowledge on target animal metabolism and residue disposition of the hormones under consideration, including the synthetic hormones. The SCVPH expects that the ongoing EU research programs will provide additional data on both topics."[498]

7.390 Finally, in 2002, the SCVPH reviewed both the 2000 Opinion and the 1999 Opinion and found that review of the 17 studies launched by the European Commission and recent scientific literature allowed the following conclusions:

(a) Ultra-sensitive methods to detect residues of hormones in animal tissues had become available, but needed further validation.

[497] 1999 Opinion, p. 73, Exhibit CDA-2.
[498] 2000 Opinion, p. 4, Exhibit CDA-4.

(b) Studies on the metabolism of oestradiol-17β in bovine species indicated the formation of lipoidal esters, disposed particularly in body fat. These lipoidal esters showed a high oral bioavailability[499] in rodent experiments. Thus, the consequence of their consumption needed to be considered in a risk assessment.

(c) Experiments with heifers, one of the major target animal groups for the use of hormones, indicated a dose-dependent increase in residue levels of all hormones, particularly at the implantation sites. Misplaced implants and repeated implanting, which seemed to occur frequently, represented a considerable risk that highly contaminated meats could enter the food chain. There was also a dose-dependent increase in residue levels following the oral administration of melengestrol acetate at doses exceeding approved levels, with a corresponding increased risk that contaminated meats could enter the food chain.

(d) Convincing data had been published confirming the mutagenic and genotoxic potential of oestradiol-17β as a consequence of metabolic activation to reactive quinones. *In vitro*[500] experiments indicated that oestrogenic compounds *might* alter the expression of an array of genes. Considering that endogenous oestrogens also exerted these effects, the data highlighted the diverse biological effects of this class of hormones.

(e) No new data regarding testosterone and progesterone relevant to bovine meat or meat products were available. However, it was emphasized that these natural hormones were used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations.

(f) Experiments with zeranol and trenbolone acetate suggested a more complex oxidative metabolism than previously assumed. These data needed further clarification as they might influence a risk assessment related to tissue residues of these compounds.

(g) Zeranol and trenbolone acetate had been tested for their mutagenic and genotoxic potential in various systems with different endpoints. Both compounds exhibited only very weak effects.

(h) Data on the genotoxicity of melengestrol acetate indicated only weak effects. However, pro-apoptotic effects were noted in some cell-based assays, which were attributed to the impurities in commercial formulation. Further experiments should clarify the toxicological significance of these impurities.

(i) Model experiments with rabbits treated with zeranol, trenbolone acetate or melengestrol acetate, mirroring their use in bovines, were designed to study the consequences of pre- and perinatal exposure to exogenous hormones. All compounds crossed the placental barrier easily and influenced to varying degrees the development of the foetus, at the doses used in the experiments.

[499] Bioavailability is the capacity of a substance to enter the general blood circulation and to diffuse into the whole body of the animal or the human being administered this substance, or the fraction of a dose of a substance that is available for systemic circulation (replies of Dr. Boisseau, Dr. Boobis and Dr. Guttenplan to Panel question 43 to the experts, Annex D, paras. 344-357).

[500] *In vitro* means outside of the body, usually in a cell-based system in a test tube or culture dish. (Transcript of the Panel meeting with the experts, Annex G, para. 96 (Dr. Boobis)).

(j) Epidemiological studies with opposite-sexed twins suggested that the exposure of the female co-twin *in utero* to hormones resulted in an increased birth weight and consequently an increased adult breast cancer risk.

(k) Several studies were devoted to the potential impact of the extensive use of hormones on the environment. Convincing data were presented indicating the high stability of trenbolone and melengestrol acetate in the environment, whereas preliminary data were provided on the potential detrimental effects of hormonal compounds in surface water.

7.391 After re-appraisal of the data from the 17 studies and recent scientific literature, the SCVPH confirmed the validity of its previous Opinions (in 1999 and 2000) on the Assessment of Potential Risks to Human Health from Hormone Residues in Bovine Meat and Meat Products, and that no amendments to those opinions were justified.[501]

7.392 A year and a half later, the European Parliament and the Council of the European Union amended Directive 96/22/EC, which was the subject of the original *EC – Hormones* dispute, by adopting Directive 2003/74/EC. In Directive 2003/74/EC, the European Communities restated the SCVPH assessment that "recent evidence suggests that [oestradiol-17β] has to be considered as a complete carcinogen, as it exerts both tumour-initiating and tumour-promoting effects and that the data currently available do not make it possible to give a quantitative estimate of the risk."[502]

7.393 The European Communities went on to conclude in its amended Directive that oestradiol-17β "can potentially be used in all farm animals and residue intake for all segments of the human population and in particular the susceptible groups at high risk can therefore be especially relevant. The avoidance of such intake is of absolute importance to safeguard human health."[503]

7.394 Finally, the European Communities concluded that in order to achieve its chosen level of protection from the risks posed, in particular to human health, by the routine use of these hormones for growth promotion and the consumption of residues found in meat derived from animals to which these hormones have been administered for growth promotion, it was necessary to maintain the permanent prohibition laid down in Directive 96/22/EC on oestradiol-17β, and provisionally ban the other five hormones at issue.

(ii) Scope of the Panel review

7.395 Given the particular circumstances under which we engage in a review of the compatibility of the EC implementing measure with the *SPS Agreement*, we deem it necessary to clearly circumscribe the scope of our review under that Agreement.

7.396 Indeed, the EC claim of violation of Article 22.8 of the DSU by Canada is premised on the alleged compatibility of the EC implementing measure with the *SPS Agreement*. We note in this respect that the European Communities itself stated in its first written submission that:

> "The new Directive provides that the use for animal growth promotion of one of the six hormones in dispute is permanently prohibited while the use of the other five is provisionally forbidden. It is based on a comprehensive risk assessment and, thus, is fully compliant with the DSB recommendations and rulings. In particular, as stipulated by the Appellate Body, the results of the risk assessment "sufficiently

[501] 2002 Opinion, pages 21-22 (Exhibit CDA-7).
[502] EC Directive 2003/74/EC.
[503] Directive 2003/74/EC, whereas clause 9.

> warrant" the definite import prohibition regarding one of the hormones (Article 5.1 of the *SPS Agreement*),[504] and provide the "available pertinent information" on the basis of which the provisional prohibition regarding the other five hormones has been enacted (Article 5.7 of the *SPS Agreement*). Consequently, through Directive 2003/74/EC the European Communities has implemented the rulings and recommendations in the *Hormones* case."[505]

7.397 In its subsequent submissions, the European Communities has argued the compatibility of its implementing measure with the provisions referred to in this quotation (i.e. Article 5.1 and 5.7).

7.398 We note that Canada argues an incompatibility of the EC implementing measure with Article 5.1 with respect to the import ban relating to meat and meat products treated with oestradiol-17β. Canada also alleges an incompatibility of the EC implementing measure with Article 5.7 with respect to the provisional import ban on meat and meat products treated with testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate. Canada also argues that the European Communities has not demonstrated that the relevant international standards for hormone growth promoters are insufficient to achieve its appropriate level of protection and thus breaches Article 3.3 of the *SPS Agreement*.

7.399 As already mentioned above, we consider that we must determine whether the European Communities has removed the measure found to be inconsistent with the covered agreement or has provided a solution to the nullification or impairment of benefits. Therefore, we conclude that we need to review the EC measure against (a) the recommendations and rulings of the DSB in the *EC – Hormones* case and (b) the provisions which the European Communities claims to comply with as part of its claim of violation of Article 22.8 of the DSU by Canada.

7.400 We also agree with the European Communities that it is difficult for the complainant in a case like this one to identify all potential problems of incompatibility. We see other difficulties if, in cases like this one where a finding of violation by a Member is conditioned by the compliance of a measure of the complainant with the WTO Agreement, the scope of review of that measure is defined only by the complainant. Indeed, the complainant could limit the scope of the panel review to provisions with which it believes that its measure is most likely to be found compatible.

7.401 In that context, we find it preferable, both from a legal and a practical point of view, to consider *all* the allegations and arguments raised by each party, as long as the other party had the opportunity to comment on those allegations and arguments.[506] We note that Canada originally argued that the European Communities breached Article 5.1 and 5.7 of the *SPS Agreement*. In its second submission, it also argued a violation of Article 3.3 of the *SPS Agreement* but, unlike the United States in WT/DS320, Canada did not raise any argument in relation to a violation of other paragraphs of Article 5 of the *SPS Agreement*.

7.402 We conclude that we shall review, to the extent necessary, the compatibility of the EC implementing measure with Articles 5.1, 5.7 and 3.3 of the *SPS Agreement*. We therefore proceed with a review of the compatibility of the EC implementing measure with those provisions in the following sections, once we have addressed other procedural issues.

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[504] The European Communities refers to the Appellate Body Report on *EC – Hormones*, para. 253 lit. (l).

[505] EC's first written submission, para. 17.

[506] We are aware of the risk that the responding party may make a new allegation of violation at a late stage of the proceedings, thus making it difficult for the complainant to reply to this allegation. We nonetheless consider that such a circumstance will not have any impact on due process as long as the complaining party is given sufficient opportunities to comment.

(iii) Standard applicable to the review of the compatibility of the EC implementing measure with the SPS Agreement

7.403 We believe that, in light of the importance and complexity of the scientific information provided by the parties and the experts, it is necessary to lay down the way we plan to review all this information.

7.404 As recalled by the Appellate Body in *EC – Hormones*, the standard of review applicable to legal and factual issues regarding measures reviewed against the *SPS Agreement* is found in Article 11 of the DSU which reads in relevant part that "... a panel should make an objective assessment of the matter before it, including an objective assessment of the facts of the case".

7.405 In *EC – Hormones*, the Appellate Body recalled that:

> "So far as fact-finding by panels is concerned, their activities are always constrained by the mandate of Article 11 of the DSU; the applicable standard is neither *de novo* review as such, nor "total deference", but rather "the objective assessment of the facts."[507]

7.406 The Appellate Body further noted that "under current practice and systems, [panels] are in any case poorly suited to engage in such a [*de novo*] review."[508]

7.407 We note that we have a duty to consider the evidence presented to us and to make factual findings on the basis of that evidence. It is also generally within our discretion to decide which evidence we choose to utilise in making findings.[509] Likewise, a panel is not expected to refer to all statements made by the experts advising it and should be allowed a substantial margin of discretion as to which statements are useful to refer to explicitly[510] as long as we do not deliberately disregard or distort evidence.[511]

7.408 We also recall that we consulted six scientific experts individually, and not as an expert review group. This may have some consequences in terms of the sometimes diverging views which they expressed. We note that, in *EC – Hormones*, the Appellate Body considered with respect to divergent views taken into account in risk assessment that:

> "We do not believe that a risk assessment has to come to a monolithic conclusion that coincides with the scientific conclusion or view implicit in the SPS measure. The risk assessment could set out both the prevailing view representing the "mainstream" of scientific opinion, as well as the opinions of scientists taking a divergent view. Article 5.1 does not require that the risk assessment must necessarily embody only the view of a majority of the relevant scientific community … In most cases, responsible and representative governments tend to base their legislative and administrative measures on "mainstream" scientific opinion. In other cases, equally responsible and representative governments may act in good faith on the basis of what, at a given time, may be a divergent opinion coming from qualified and respected sources. By itself, this does not necessarily signal the absence of a reasonable relationship between the SPS measure and the risk assessment, especially where the risk involved is life-threatening in character and is perceived to constitute a

[507] Appellate Body Report on *EC – Hormones*, para. 117.
[508] Appellate Body Report on *EC – Hormones*, para. 117.
[509] Appellate Body Report on *EC – Hormones*, para. 135.
[510] Appellate Body Report on *EC – Hormones*, para. 138.
[511] Appellate Body Report on *EC – Hormones*, para. 139.

> clear and imminent threat to public health and safety. Determination of the presence or absence of that relationship can only be done on a case-to-case basis, after account is taken of all considerations rationally bearing upon the issue of potential adverse health effects."[512]

7.409 Although the Panel is not carrying out its own risk assessment, its situation is similar in that it may benefit from hearing the full spectrum of experts' views and thus obtain a more complete picture both of the mainstream scientific opinion and of any divergent views.

7.410 Likewise, in *EC – Asbestos*, the Appellate Body stated that:

> "In justifying a measure under Article XX(b) of the GATT 1994, a Member may also rely, in good faith, on scientific sources which, at that time, may represent a divergent, but qualified and respected, opinion. A Member is not obliged, in setting health policy, automatically to follow what, at a given time, may constitute a majority scientific opinion. Therefore, a panel need not, necessarily, reach a decision under Article XX(b) of the GATT 1994 on the basis of the "preponderant" weight of the evidence."[513]

7.411 We note that, in some circumstances, only one or two experts have expressed their views on an issue. Sometimes these views were similar or complemented each other. In other circumstances, a larger number of experts expressed opinions and, sometimes, they expressed diverging opinions. While, on some occasions, we followed the majority of experts expressing concurrent views, in some others the divergence of views were such that we could not follow that approach and decided to accept the position(s) which appeared, in our view, to be the most specific in relation to the question at issue and to be best supported by arguments and evidence. As we have told the parties and the experts during these proceedings, this Panel is not composed of scientists.[514] The experts were also made fully aware of their role – which was *inter alia* to present scientific issues to the Panel members in a way that could be understood by them – and of the role of the Panel in the WTO dispute settlement system – which is *inter alia* one of trier of fact. In assessing the scientific advice received from the experts, we also fully took into account the comments of the parties, when appropriate.

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[512] Appellate Body Report on *EC – Hormones*, para. 194.
[513] Appellate Body Report on *EC – Asbestos*, para. 178.
[514] In the letter sent to the experts in relation to the preparation of their written replies, the Panel made the following remark:

> "In drafting your replies, please remember that the three panelists serving on the case have no scientific background and are trying to digest the extensive scientific material submitted by the parties with your help. Therefore, please provide concise answers which clarify the issues at hand and which will eventually assist the Panel in reaching its legal findings." (Emphasis in the original)
>
> Likewise, at the outset of the meeting with the experts, the Chairman mentioned the following:
>
> "Last but not least, I would like to recall that the Panel members do NOT have scientific expertise. Therefore, I would like to ask the experts to bear this in mind in replying to questions and explain issues in layman's terms, providing information on underlying concepts as necessary. In order to get a clearer picture with respect to each of the six hormones at issue, I would also like to invite all those taking the floor to clarify which of the six hormones their question or reply applies to."

However, as already mentioned, we disregarded those comments that attempted to put into question the objectivity of specific experts. We believe that such questions had to be dealt with separately.[515]

7.412 We also recall that we are expected to make findings with respect to each of the hormones concerned. Indeed, in *Japan – Apples*, the Appellate Body recalled that findings should be made for each precise agent that may possibly cause the harm (in this case each of the hormones concerned):

> "Under the *SPS Agreement*, the obligation to conduct an assessment of 'risk' is not satisfied merely by a general discussion of the disease sought to be avoided by the imposition of a phytosanitary measure. The Appellate Body found the risk assessment at issue in *EC — Hormones* not to be 'sufficiently specific' even though the scientific Articles cited by the importing Member had evaluated the 'carcinogenic potential of entire *categories* of hormones, or of the hormones at issue *in general*.' In order to constitute a 'risk assessment' as defined in the *SPS Agreement*, the Appellate Body concluded, the risk assessment should have reviewed the carcinogenic potential, not of the relevant hormones in general, but of 'residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes'. Therefore, when discussing the risk to be specified in the risk assessment in *EC – Hormones*, the Appellate Body referred in general to the harm concerned (cancer or genetic damage) *as well as* to the precise agent that may possibly cause the harm (that is, the specific hormones when used in a specific manner and for specific purposes)."[516]

7.413 We will therefore address the compatibility of the EC implementing measure with respect to each hormone concerned, as appropriate. However, in situations where, for instance, information and evidence are similar for all hormones, or where information was not provided for each hormone in spite of our insistence, specific issues are addressed with respect to the hormones concerned as a whole.

7.414 There is another question raised in these proceedings which the Panel believes it must address at this stage. It is the issue of "old" versus "new" evidence, data or studies. Indeed, the European Communities relied extensively on the date of the evidence relied upon by JECFA to support its view that the risk assessments performed by JECFA are outdated and the ensuing recommendations of Codex unreliable.

7.415 In its submissions before the Panel and during the hearing with the scientific experts, the European Communities contested the validity of JECFA's findings[517] on the basis that it had relied in its assessments on studies that dated back to the 1960s, 1970s and 1980s. The Panel sought the views of the experts on this point.[518] Dr. Boisseau pointed out that "It is just a banality to say that JECFA is provided with new data when it is requested to assess veterinary drugs recently placed on the market and older data in the case of veterinary drugs already marketed since a long time ago. Anyway, the quality and the number of the available data are more important than the dates at which these data have been produced."[519]

7.416 During the hearing with the experts, the European Communities sought the view of Dr. De Brabander as to whether the validity of "old" data from the 1970s and 1980s should be put in doubt

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[515] See Section VII.A.2(c) above.

[516] Appellate Body Report on *Japan – Apples*, para. 202 (original footnotes omitted).

[517] For a comprehensive list and explanation of JECFA's risk assessment on the six hormones concerned, *see* Annex E-2, JECFA's reply to Panel question 17, as well as Exhibit CDA-32.

[518] See questions 34 and 35 of the Panel to the scientific experts, Annex D.

[519] Reply of Dr. Boisseau to question 35 of the Panel, Annex D.

because they are old and they have been measured with measurement methods which, it argues, are by today's standards not credible, are not accurate, because there are new, more powerful and more accurate analytical methods.[520] Dr. De Babander replied: "[t]hat is my conclusion. I cannot say that the data are bad, I don't say that, I just say you don't know that they are good."[521]

7.417 During the same hearing, Dr. Wennberg specified that: "... even if [the studies used by JECFA] were older [than the 1970s], if the methodology that was used, and if the methods had been validated properly, there is no reason to discredit any studies because they were done a long time ago."[522] Dr. Boisseau added that:

> "What the Commission said is true as regards the results that are at the level of the limits of detection of the methods previously used. But once the results obtained are clearly over the limits of detection, what counts is the precision of the method and its reproducibility. The fact that the method used to provide these results is old is irrelevant to the extent that they have been validated. Indeed, we need only concern ourselves with the uncertainty that we may have regarding the very low values at the level of the limits of detection."[523]

7.418 The Panel first notes that the experts agree that data do not become invalid only because they are old, but that more recent measurement or analytical methods may be more accurate. The Panel notes, however, that a problem related to accuracy is likely to occur with respect to results at the level of the detection limits of the older methods. Outside this particular situation, what matters is whether the method has been validated. The Panel thus concludes that whether a study is old or not is not *per se* a criterion to put in doubt the validity of this study.

(iv) Whether the EC implementing measure is an SPS measure

7.419 Before the Panel can determine whether the EC ban is consistent with the *SPS Agreement*, we must first determine whether the measure is subject to the disciplines of the *SPS Agreement*, *i.e.* whether the measure is an SPS measure. In order to determine whether the ban is an SPS measure, the Panel will determine whether the measure fits within the definition of an SPS measure set forth in Annex A(1) of the *SPS Agreement*.[524]

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[520] Transcript of the Panel meeting with the experts, Annex G, para. 674.
[521] Transcript of the Panel meeting with the experts, Annex G, para. 675.
[522] Transcript of the Panel meeting with the experts, Annex G, para. 651.
[523] Transcript of the Panel meeting with the experts, Annex G, para. 679.
[524] Article 1 of the *SPS Agreement* reads as follows:

> "General Provisions
>
> 1. This Agreement applies to all sanitary and phytosanitary measures which may, directly or indirectly, affect international trade. Such measures shall be developed and applied in accordance with the provisions of this Agreement.
>
> 2. For the purposes of this Agreement, the definitions provided in Annex A shall apply.
>
> 3. The annexes are an integral part of this Agreement.
>
> 4. Nothing in this Agreement shall affect the rights of Members under the Agreement on Technical Barriers to Trade with respect to measures not within the scope of this Agreement."
>
> Annex A, paragraph 1, to the *SPS Agreement* reads as follows:

7.420 As the panel in *EC – Approval and Marketing of Biotech Products* explained, in determining whether a measure is an SPS measure, regard must be had to such elements as the purpose of the measure, its legal form and its nature. The purpose element is addressed in Annex A(1)(a) through (d) ("any measure applied to"). The form element is referred to in the second paragraph of Annex A(1) ("laws, decrees, regulations"). Finally, the nature of measures qualifying as SPS measures is also addressed in the second paragraph of Annex A(1) ("requirements and procedures, including, inter alia, end product criteria; processes and production methods; testing, inspection, certification and approval procedures; [etc.]"). The Panel will address each element hereafter.

7.421 The European Communities explained in Directive 2003/74/EC that the purpose of the ban on the six hormones at issue is to prevent meat and meat products from cattle treated with such hormones for growth promotion purposes from being placed on the EC market.[525] The Panel notes that Annex A(1)(b) defines an SPS measure as any measure applied "to protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs."

7.422 Consistent with the Panel in *EC– Approval and Marketing of Biotech Products* we consider that a substance which a human being or an animal consumes for nutritional reasons may be classified as a "food".[526] The Panel also takes notice of the footnote to Annex A, which specifically defines "contaminants" as including veterinary drug residues, such as the residues of the hormones which are the subject of the EC measure.

DEFINITIONS [footnote 4]

"1. Sanitary or phytosanitary measure – Any measure applied:

(a) to protect animal or plant life or health within the territory of the Member from risks arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms;

(b) to protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs;

(c) to protect human life or health within the territory of the Member from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; or

(d) to prevent or limit other damage within the territory of the Member from the entry, establishment or spread of pests.

Sanitary or phytosanitary measures include all relevant laws, decrees, regulations, requirements and procedures including, inter alia, end product criteria; processes and production methods; testing, inspection, certification and approval procedures; quarantine treatments including relevant requirements associated with the transport of animals or plants, or with the materials necessary for their survival during transport; provisions on relevant statistical methods, sampling procedures and methods of risk assessment; and packaging and labelling requirements directly related to food safety."

Footnote 4 to Annex A reads as follows:

"For the purpose of these definitions, "animal" includes fish and wild fauna; "plant" includes forests and wild flora; "pests" include weeds; and "contaminants" include pesticide and veterinary drug residues and extraneous matter."

[525] Directive 2003/74/EC, Article 1.

[526] Panel Report on *EC – Approval and Marketing of Biotech Products*, paras. 7.291-7.292.

7.423 Comparing the definition of an SPS measure in Annex A(1)(b) to the stated purpose of the EC ban on the hormones at issue, the Panel concludes that the purpose of the EC measure is that of an SPS measure within the meaning of Annex A(1)(b) of the *SPS Agreement*.

7.424 The second paragraph of Annex A states that sanitary or phytosanitary measures include all relevant laws, decrees and regulations as well as requirements and procedures.[527] In this instance, the EC measure is a directive adopted by the Council of the European Union and the European Parliament which was published in the Official Journal of the European Communities. Therefore, this Panel finds that the measure in question is included within the phrase "all relevant laws, decrees, regulations ..." as used in Annex A of the *SPS Agreement*. This Panel also agrees with the panel in *EC– Approval and Marketing of Biotech Products* that a ban may be considered as a "requirement" within the meaning of the second paragraph of Annex A to the *SPS Agreement*.[528] Therefore, this Panel finds that the EC measure constitutes such a "requirement".

7.425 In conclusion, because the EC Directive 2003/74/EC was adopted for the purpose of protecting human life from contaminants in food and takes the form and nature contemplated in the second paragraph of Annex A, this Panel finds that the EC Directive 2003/74/EC is an SPS measure within the meaning of Annex A(1)(b) and the second paragraph of Annex A.

(e) Compatibility of the EC implementing measure with Article 5.1 of the *SPS Agreement* with respect to oestradiol-17β

(i) Introduction

7.426 The Panel notes that the European Communities has asserted that it adopted the Directive banning the placing on the market of meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes based on a risk assessment conducted by the SCVPH consistent with Article 5.1 of the *SPS Agreement*.

7.427 Specifically, the European Communities states that in order to comply with the rulings and recommendations of the DSB in the *EC – Hormones* dispute, it conducted a comprehensive risk assessment, which focused on potential risks to human health from hormone residues in bovine meat and meat products.[529] The European Communities also asserts that Directive 2003/74/EC, which provides for a permanent ban on meat and meat products from animals treated for growth promotion purposes with oestradiol-17β, is based on the above referenced risk assessment.[530]

7.428 We note that the DSB found in the *EC – Hormones* dispute that the ban on meat and meat products from cattle treated with the six hormones for growth promotion purposes, according to good veterinary practice ("GVP"), was inconsistent with Article 5.1 of the *SPS Agreement* because it was not based on a risk assessment within the meaning of that Article. In this case, the European Communities has asserted that it has removed that inconsistency with respect to oestradiol-17β by conducting a comprehensive risk assessment and basing its implementing measure on that risk assessment so that the measure is now consistent with Article 5.1 of the *SPS Agreement*. We also recall that, unlike the United States in dispute WT/DS320, Canada has not argued that the EC definitive ban on oestradiol-17β breaches Article 5.2 of the *SPS Agreement*, but only that it breaches

[527] "Including *inter alia* end product criteria; processes and production methods; testing, inspection, certification and approval procedures; quarantine treatments including relevant requirements associated with the transport of animals or plants, or with the materials necessary for their survival during transport; provisions on relevant statistical methods, sampling procedures and methods of risk assessment; and packaging and labelling requirements directly related to food safety."

[528] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.1334.

[529] EC's first written submission, para. 143.

[530] EC's first written submission, para. 146.

Article 5.1. Therefore, as mentioned above, the Panel considers that it should limit its review of the conformity of the EC implementing measure to Article 5.1 of the *SPS Agreement*.

7.429 Article 5.1 of the *SPS Agreement* reads as follows:

> "Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations."

7.430 An analysis under Article 5.1 consists of two fundamental questions. First, was a risk assessment, appropriate to the circumstances and taking into account risk assessment techniques developed by the relevant international organizations conducted? Second, is the sanitary measure based on that risk assessment? The Panel will address each question successively.

(ii) Is there a risk assessment within the meaning of Article 5.1 of the SPS Agreement?

7.431 In assessing whether a measure is based on a risk assessment within the meaning of Article 5.1 of the *SPS Agreement*, the Panel must first determine whether a risk assessment was conducted at all. The Panel is aware that the Appellate Body in *EC – Hormones* determined that "Article 5.1 does not insist that a Member that adopts a sanitary measure shall have carried out its own risk assessment … The SPS measure might well find its objective justification in a risk assessment carried out by another Member, or an international organization".[531] In the present case, the European Communities has asserted that the three Opinions produced by the SCVPH, an organ of the European Communities, constitute the required risk assessment. Therefore, the task before the Panel is to determine whether the European Communities conducted a risk assessment within the meaning of Article 5.1 of the *SPS Agreement*.

7.432 To determine whether the Opinions constitute a risk assessment, the Panel must measure the European Communities' actions against the requirements of the *SPS Agreement*. The Panel recalls that it is not the appropriate role of the Panel to conduct its own risk assessment based on scientific evidence gathered by the Panel or submitted by the parties during the Panel proceedings.[532] Similarly, the Panel believes that it is not its role to impose any scientific opinion on the European Communities.[533] The Panel must objectively measure the Opinions against the relevant standard for whether a risk assessment has been conducted, which can be found in the texts of Article 5.1 as well as Annex A(4) of the *SPS Agreement*. Therefore, we examined and evaluated the evidence – including the information received from the experts advising the Panel – and the arguments put before us in light of the relevant WTO provisions and based our conclusions on this evidence and these arguments.[534]

7.433 The text of Article 5.1 requires that in the assessment of risks the Members take into account risk assessment techniques developed by the relevant international organizations. Article 5.2, likewise, prescribes several factors that a Member must take into account when making its assessment of the risks. Additionally, Annex A(4) provides a definition of what constitutes a risk assessment.

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[531] Appellate Body Report on *EC – Hormones*, para. 190, followed in the Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.3024.

[532] Panel Report on *EC – Hormones (Canada)*, para. 8.104; Panel Report on *EC – Hormones (US)*, para. 8.101.

[533] Panel Report on *Australia – Salmon*, para. 8.41. A similar statement was made by the Panel on *Japan – Agricultural Products II*, in para. 8.32.

[534] Panel Report on *Australia – Salmon*, para. 8.41. A similar statement was made by the Panel on *Japan – Agricultural Products II*, in para. 8.42.

Finally, as the Panel and Appellate Body explained in *Japan – Apples*, for a risk assessment to be valid the science evaluated must support the conclusions reached in the risk assessment.[535]

7.434 The European Communities asserts that the 1999, 2000, and 2002 Opinions constitute its risk assessment for oestradiol-17β. Therefore, in determining whether these Opinions are indeed a risk assessment as appropriate to the circumstances, within the meaning of Article 5.1 of the *SPS Agreement*, the Panel will examine whether the Opinions (1) took into account risk assessment techniques of the relevant international organizations; (2) satisfied the definition in Annex A(4) and: (3) whether the conclusions in the Opinions are supported by the scientific evidence evaluated.

Do the Opinions take into account risk assessment techniques of the relevant international organizations?

Introduction

7.435 Article 5.1 includes the proviso that Members, when developing sanitary and phytosanitary measures based on risk assessments, take into account risk assessment techniques developed by the relevant international organizations. The *SPS Agreement* does not specifically identify the relevant international organizations for purposes of Article 5.1. However, the Preamble of the *SPS Agreement* speaks of harmonization and recommendations developed by the relevant international organizations, including the Codex Alimentarius Commission (Codex). Additionally, Annex A(3) states that for food safety the standards, guidelines and recommendations established by the Codex Alimentarius Commission (Codex) relating to food additives, veterinary drug and pesticide residues, contaminants, methods of analysis and sampling, and codes and guidelines of hygienic practice will constitute international standards, guidelines, and recommendations within the meaning of the *SPS Agreement*. Article 3.2 states that SPS measures which conform to the above referenced standards are deemed to be necessary to protect human, animal, or plant life or health and are presumed to be consistent with the *SPS Agreement* and *GATT 1994*. Moreover, Article 3.4 of the *SPS Agreement* requires Members to participate fully in Codex work, within the limits of their resources. After an examination of these provisions of the *SPS Agreement* and the context of Article 5.1 as part of the process for adopting SPS measures which are consistent with the *SPS Agreement*, the Panel concludes that the Codex Alimentarius Commission constitutes a "relevant international organization" within the meaning of Article 5.1.

7.436 The parties in this dispute as well as the experts have made significant references to JECFA's work. JECFA, while officially not part of the Codex structure, provides independent scientific expert advice to the Codex Alimentarius Commission and its specialist Committees. JECFA conducts risk assessments on various substances, establishes ADIs[536] where appropriate, and in the case of residues of veterinary drugs in foods, recommends MRLs[537] for consideration by the Codex Committee on

[535] This is not to say, as already recalled above, that a risk assessment cannot be based on a minority opinion of the scientists. A risk assessment can be based on a minority opinion which is supported by sufficient scientific evidence. See Appellate Body Report on *EC-Hormones*, para. 194; and Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.3240.

[536] The Codex Committee on Residues of Veterinary Drugs in Foods defines an Acceptable Daily Intake (ADI) as "[a]n estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg)." Glossary of Terms and Definition (CAC/MISC 5-1993). The "Glossary of Terms and Definition" has been elaborated by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) with a view to providing information and guidance to the committee and is intended for internal Codex use only. (The definition was previously established and adopted by JECFA and modified by the Codex Committee on Veterinary Drugs in Foods). More information on how ADIs are set is contained in Annex E-2, responses by JECFA to questions 9 and 10.

[537] Codex defines the maximum limit for residues of veterinary drugs (MRLVD) as the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh

Residues of Veterinary Drugs in Foods (CCRVDF). The MRLs adopted by Codex with respect to oestradiol-17β and four of the other five hormones[538] are based on the recommendations of JECFA. Therefore, this Panel believes that the risk assessment techniques of JECFA are also relevant to an analysis of compliance with Article 5.1.

7.437 Codex and JECFA have developed definitions of the relevant phases of a risk assessment as well as guidelines and practices for conducting a risk assessment.[539] The European Communities indicated in the 1999 Opinion, that the accepted definition of a risk assessment, as used by both Codex and JECFA, is an assessment which is "structured to address independently the intrinsic properties of the compound under consideration (hazard identification), the evaluation of the nature of effects in terms of a dose-response relationship (hazard characterization), the estimate of the dose/concentration of a compound in a daily diet (exposure assessment) resulting in the assessment of the incidence and severity of potential adverse effects."[540] In its Procedural Manual, Codex defines the four phases of risk assessment as follows:

(a) *hazard identification*: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

(b) *hazard characterization*: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical, and physical agents which may be present in food. For chemical agents, a dose-response assessment[541] should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.

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weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.

It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.

When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available. From: Definitions for the Purposes of the Codex Alimentarius, Codex Alimentarius Commission Procedural Manual (15th Edition), FAO and WHO, 2006, page 43. More information on how MRLs are set is contained in Annexes E-1 and E-2, responses by Codex and JECFA to questions 9 and 10.

[538] Progesterone, testosterone, zeranol and trenbolone acetate. (http://www.codexalimentarius.net/mrls/vetdrugs/jsp/vetd_q-e.jsp).

[539] In response to the Panel's questions regarding international guidance documents for conducting a risk assessment, in particular with respect to veterinary drug residues, the representative of Codex and JECFA as well as the experts referred to a variety of documents from the Codex Alimentarius Commission, JECFA, the World Health Organization, the Food and Agriculture Organization, and other scientific bodies, see Responses of the Codex Alimentarius Commission and JECFA to Panel Questions 3 and 4, Annexes E-1 and E-2 respectively and replies by the scientific experts to Panel questions, Annex D, paras. 62-71.

[540] 1999 Opinion, page 70, Exhibit CDA-2.

[541] Codex defines a dose-response assessment as the determination of the relationship between the magnitude of exposure (dose) to a chemical, biological, or physical agent and the severity and/or frequency of associated adverse health effects (response). *Codex Alimentarius Commission*, Procedural Manual, Fifteenth Edition (2005), p. 45.

(c) *exposure assessment*: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, or physical agents via food as well as exposures from other sources if relevant.

(d) *risk characterization***:** The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known potential adverse health effects in a given population based on hazard identification, hazard characterization, and exposure assessment.[542]

7.438 Although Codex and JECFA base their relevant work on some general principles and the definitions of a risk assessment stated above and JECFA relies on a variety of guidance documents on how to conduct a risk assessment with respect to veterinary drug residues in food, the experts confirmed that no specific "techniques" or guidelines had thus far been adopted by Codex for use by national governments in conducting risk assessments of veterinary drug residues.[543]

Summary of the main arguments of the parties[544]

7.439 **Canada** argues that, while the requirement of Article 5.1 that the risk assessment relied upon by the European Communities "tak[e] into account risk assessment techniques developed by the relevant international organizations" does not amount to an obligation to conduct a risk assessment according to these techniques, an evaluation of the purported risk assessment according to these techniques provides context and guidance to the more general test elaborated by the Appellate Body in *EC – Hormones*. Canada disagrees with the EC claim that the Opinions followed these techniques.

7.440 Canada challenges the EC claim that a positive relationship between genotoxicity and the incidence of tumours may alter the approach taken in a risk assessment. Canada argues that this does not grant the European Communities licence to avoid completely the requirement that its measure be based on a valid risk assessment.

7.441 Canada also challenges the EC claim that data are unavailable to allow it to conduct an exposure assessment, noting that the scientific studies commissioned by the European Communities in fact generated exposure data. Canada notes that, in any event, other reputable scientific bodies have conducted complete assessments of risks from residues of the hormones at issue in meat from treated animals, dealing with both the issue of "non-linear situations" and that of exposure, without encountering the limitations expressed by the European Communities.

7.442 According to Canada, one further shortcoming of the SCVPH's hazard characterization is that it fails to conduct a dose-response assessment. The reasons provided by the SCVPH are that no threshold level can be established for genotoxic metabolites in meat and additionally that no threshold level can be established for "any of the hormonally active compounds and metabolites which might exert endocrinal, developmental and neurobiological, immunological or immunotoxicological effects." However, it is widely, if not universally, accepted that adverse effects arising from hormonal activity are dose-dependent. Canada argues that the SCVPH provides no justification for why this generally-accepted understanding of the dose-response relationship of hormonally active substances should be rejected a priori in these circumstances, such that it considers it unnecessary to conduct a dose-response assessment. Furthermore, while international risk assessment techniques suggest that a

[542] Ibid.

[543] At its 30th session in July 2007, the Codex Alimentarius Commission adopted "Working Principles for Risk Analysis for Food Safety for Application by Governments".

[544] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents, as is the case with the hormones at issue here.

7.443 Canada adds that, in any event, the obligation on the European Communities is to base its measure on a risk assessment that complies with the requirement under the *SPS Agreement* to evaluate the potential occurrence of adverse effects. In this respect, Canada considers that the European Communities misinterprets the Appellate Body's findings that a risk assessment under the *SPS Agreement* need not identify a minimum, quantifiable magnitude of risk by suggesting that it need not conduct quantitative analysis at any stage of the risk assessment. While the Appellate Body in *EC – Hormones* did find that the evaluation of the potential occurrence of adverse effects (that is, at the risk characterization stage) could be qualitative or quantitative, it went on to find that such evaluation still needs to be a process characterized by systematic, disciplined and objective enquiry and analysis.[545]

7.444 The **European Communities** agrees that the risk assessment techniques developed by Codex are relevant and contemplated in Article 5.1's requirement to take into account the risk assessment techniques developed by relevant international organizations.[546]

7.445 In this respect, the European Communities maintains that its Opinions take into account the conventional risk assessment techniques in addition to other factors that are expressly permissible under the definition of a risk assessment in Article 5.1.[547] The European Communities argues that it went beyond the international standards for a risk assessment to consider "real life" situations as contemplated by the Appellate Body's ruling in *EC – Hormones.*

7.446 The European Communities argues that the risk assessment at the basis of Directive 2003/74/EC precisely follows the four steps of risk assessment as defined by Codex, enabling it to identify different levels of risks presented by different uses, and that this Directive then adapts the management of these risks accordingly.[548] However, the European Communities also notes that the Codex approach has serious limitations in non-linear situations, such as with regard to these hormones. The European Communities argues that the currently available Codex guidance poorly addresses cases such as this where the risks are embedded in changes in exposure to biologically active molecules which may, with minute differences in their bioavailability, have dramatic effects, such as turning on or off complete developmental programmes of the human genome, or inducing pathological conditions.[549]

7.447 Specifically, the European Communities argued that with hormones that are also produced endogenously when you add more of the same kind of hormone, such as oestrogen, you are just increasing the response that is already taking place, and in that case there cannot be a threshold. The threshold has already been exceeded by the concentration of hormones in circulation. So this specific

[545] Canada's second written submission, para. 81.
[546] EC's replies to Panel questions after the first substantive meeting, question 24, Annex B-1.
[547] 1999 Opinion, p.2 (citing Appellate Body Report on *EC – Hormones* for the premise that the risk to be evaluated is "not only risk ascertainable in a laboratory operating under strictly controlled conditions, but also risk in human societies as they actually exist, in other words the actual potential for adverse effects in human health in the real world where people live and work and die.")
[548] EC's replies to Panel questions after the first substantive meeting, question. 24, Annex B-1, para. 142.
[549] EC's replies to Panel questions after the first substantive meeting,, question 24, Annex B-1, para. 140.

set of conditions results in dose-response curves that will have no threshold, and if there is no threshold, there is no safe dose, unlike the suggestion that there is an acceptable daily intake.[550]

7.448 The European Communities asserts that it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold cannot be identified. This would mean that there is no level below which intakes from residues should be considered to be safe. The fact that the doses used in growth promotion are low is not of relevance.[551] Therefore, the European Communities argues that it was not required to do a quantitative evaluation of the dose-response.[552]

7.449 With respect to Canada's arguments regarding identification of adverse effect, particularly Canada's argument that the new risk assessment of the European communities is not specific enough, the European Communities argues these arguments are based on outdated data from Canada and JECFA. The European Communities adds that Canada misinterprets the findings of the latest scientific evidence, including that generated by the 17 EC studies.

7.450 To Canada's argument that the findings of the SCVPH are not specific to residues in meat, the European Communities responds that the 1999 and 2002 Opinions of the SCVPH have a specific chapter for each of the six hormones about the dose-response question and the potential risks from residues in meat from animals treated with these hormones for growth promotion.[553] The European Communities notes that even JECFA has declared oestradiol-17β for the first time in 1999 to have "genotoxic potential", which means that there is normally no safe threshold for any amount of residues in meat from this hormone. So the issue of specificity for this hormone becomes irrelevant.

7.451 The European Communities further argues that Canada's argument that the SCVHP failed to complete the second step of the risk assessment in that its opinions do not evaluate the potential occurrence of the adverse effects they purport to identify is incorrect. Indeed, this refers to the exposure of consumers to hormones originating from the treatment of animals. This is referred to in the Opinions in several points.[554]

Reasoning of the Panel

7.452 In determining whether the European Communities took into account the risk assessment techniques of the relevant international organizations in the Opinions, the Panel requested that the experts evaluate the Opinions in light of the Codex definitions, guidelines, and practices.

7.453 The experts who answered the Panel's question on this issue concluded that the Opinions were not entirely consistent with the Codex guidelines and definitions.

7.454 Dr. Guttenplan pointed out that the European Communities had done a thorough hazard identification, but that its hazard characterization was limited and that the extrapolation of the one animal model study from hamster kidney to humans was uncertain. He noted that the European Communities also relied on older studies with no reports of replication and had no epidemiological studies comparing cancer incidence or prevalence in populations consuming hormone-treated or untreated meat.[555] Dr. Boobis stated that the European Communities had not identified the potential for adverse effects on human health of residues of oestradiol found in meat from treated cattle. This

[550] Transcript of the Panel meeting with the experts, Annex G, para. 252.
[551] EC's second written submission, paras. 201-202.
[552] EC's second written submission, para. 200.
[553] See section 4.1.5 for oestradiol, section 4.2.4. for testosterone, section 4.3.4. for progesterone, section 4.4.4. for trenbolone acetate, section 4.5.4. for zeranol, and section 4.6.4. for melengestrol acetate.
[554] EC's second written submission, paras. 115-127.
[555] Replies by the scientific experts to Panel question 14, Annex D, para. 149.

was because the analysis undertaken was focused primarily on hazard identification. There was little in the way of hazard characterization, and no independent exposure assessment was undertaken. Dr. Boobis stated that because no adequate exposure assessment was undertaken it was not possible to complete the risk characterization phase of the assessment.[556] In sum, Dr. Boobis concluded that the European Communities' risk assessment of oestradiol did not follow the four steps of the Codex risk assessment paradigm.[557]

7.455 Dr. Boobis indicates in his written replies that a "hazard-based" approach, which is making recommendations as to potential safety based on intrinsic capacity to cause harm rather than on the probability of harm occurring is most commonly used for substances that are genotoxic or have genotoxic potential, although not all such substances would be treated this way.[558] Dr. Boobis further explained the "hazard-based" approach at the meeting with the Panel where he stated that if, for example, a compound is shown to be a direct-acting genotoxicant, this is considered unacceptable at any level of exposure. As permitting exposure would not be appropriate, one stops the risk assessment at that point. It does not need to take account of exposure, because any level of exposure is deemed to be of concern.[559] Dr. Cogliano agrees that there have been cases where calling something a carcinogenic hazard has led an agency to make a decision just on the qualitative element alone.[560] However, Dr. Tritscher, the representative of JECFA maintains that a hazard identification is not a risk assessment; a risk assessment comprises the four steps.[561]

7.456 Both Drs. Cogliano and Boobis explain that the issue of thresholds and whether an acceptable daily intake can be established and all four steps of a risk assessment as defined by Codex can be conducted has to do with the assumptions and interpretations that the scientists conducting the risk assessment are willing to make.[562]

7.457 Although there was considerable debate among the parties and the experts advising the Panel about whether the European Communities followed all four steps of a risk assessment as defined by Codex or indeed whether it was even necessary to do so in the case of a substance such as oestradiol-17β, the Panel must concur with the reasoning of the panel in *Japan – Apples*, that the requirement to "take into account" the risk assessment techniques of international organizations:

> "[D]oes not impose that a risk assessment under Article 5.1 be 'based on' or 'in conformity with' such risk assessment techniques. This suggests that such techniques should be considered relevant, but that a failure to respect each and every aspect of them would not necessarily, *per se*, signal that the risk assessment on which the measure is based is not in conformity with the requirements of Article 5.1."[563]

7.458 This means that although the risk assessment techniques of Codex and JECFA are relevant and must be considered by the risk assessor, compliance with Codex or JECFA risk assessment techniques is not required by the *SPS Agreement*. What is required is that the risk assessor take those techniques into account and that it comply with the other requirements of Article 5 and Annex A of the *SPS Agreement* with respect to conducting a risk assessment.

7.459 It is undisputed that the European Communities was aware of the Codex and JECFA guidelines and considered them in the preparation of the Opinions. Therefore, the Panel concludes

[556] Replies by the scientific experts to Panel question 13, Annex D, para. 144.
[557] Replies by the scientific experts to Panel question 14, Annex D, para. 148.
[558] Replies by the scientific experts to Panel question 36, Annex D, paras. 310-311.
[559] Transcript of the Panel meeting with the experts, Annex G, para. 385.
[560] Transcript of the Panel meeting with the experts, Annex G, para. 438.
[561] Transcript of the Panel meeting with the experts, Annex G, para. 453.
[562] Transcript of the Panel meeting with the experts, Annex G, paras. 1021-1027.
[563] Panel Report on *Japan – Apples*, para. 8.241.

that although it may not have strictly followed them, the European Communities did take into account the risk assessment techniques of the relevant international organizations in the conduct of the Opinions.

Do the Opinions satisfy the definition in Annex A(4) of the *SPS Agreement*?

Introduction

7.460 Annex A(4) defines a risk assessment as:

> "[t]he evaluation of the likelihood of entry, establishment or spread of a pest or disease within the territory of an importing Member according to the sanitary or phytosanitary measures which might be applied, and of the associated potential biological and economic consequences; *or the evaluation of the potential for adverse effects on human or animal health arising from the presence of additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs.*" (Emphasis added)

7.461 In this dispute, the measure at issue is intended to protect human health as a sanitary measure defined in Annex A(1)(b) and, thus, is to be based on a risk assessment in the sense of the second definition in Annex A(4).[564]

Summary of the main arguments of the parties[565]

7.462 **Canada** argues that the three Opinions do not constitute a "risk assessment" for the purposes of the *SPS Agreement*. The Opinions do not identify any adverse effects on human health that arise from the consumption of meat containing residues of oestradiol-17β that has been used as a growth promotant. The Opinions identify only in a speculative fashion potential adverse effects of oestradiol-17β in general, a substance available from many sources both endogenous and exogenous. The opinions identify no adverse effects arising from oestradiol-17β when used as a growth promotant.

7.463 According to Canada, none of the potential adverse effects identified by the SCVPH, however, were said to arise specifically from the consumption of meat containing residues of oestradiol-17β when used as a growth promotant. In fact, the SCVPH specifically acknowledges on several occasions the absence of such a link. Therefore, as a result of the speculative nature of the identification of potential adverse effects in general and the absence of a specific link between such effects and the use of hormone growth promotants in particular, the Opinions cannot be seen to satisfy the first condition of a "risk assessment".

7.464 Canada also argues that the SCVPH has further failed to complete the second step in that its opinions do not evaluate the potential occurrence of the adverse effects they purport to identify. The Opinions simply point to general concerns about possible adverse effects of oestradiol-17β, and do not evaluate the potential occurrence of such effects as a result of consumption of meat derived from hormone-treated animals. This failure is a function of having not sufficiently identified any adverse effects from the consumption of meat derived from animals treated with oestradiol-17β, making it

[564] Panel Report on *Australia – Salmon*, paras. 8.72 and 8.116 (that panel finds that because the measure at issue was meant to protect animal health as a sanitary measure as defined in Annex A(1)(a), the first definition in Annex A(4) applied).

[565] A more detailed account of the parties' arguments can be found in Section IV the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

impossible to evaluate the potential that such adverse effects will occur. More importantly, however, the SCVPH has failed to conduct even the minimum steps of such an evaluation.

7.465 Canada recalls that the Appellate Body found in *EC – Hormones* that the scientific evidence considered in a risk assessment had to be "sufficiently specific" to the substance at issue, in this case residues of oestradiol-17β in meat from animals that have been treated with that substance for growth-promotion purposes. Even for those potential adverse effects that it does identify the SCVPH does not evaluate in a manner that is sufficiently specific to the substances at issue, and as such the SCVPH has not completed the second step required of a risk assessment.[566]

7.466 The **European Communities** argues that the Opinions do constitute a risk assessment within the meaning of Article 5.1 of the *SPS Agreement*. Specifically, the European Communities argues that there is a difference between a scientific risk assessment in the narrow sense referred to by Canada and the risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*.[567]

7.467 The European Communities argues that the Appellate Body has confirmed that a risk assessment within in the meaning of Article 5.1 includes a risk management stage which is the responsibility of the regulator to carry out and not of the scientific bodies.[568]

7.468 Although the European Communities agrees that in principle the risk resulting from human consumption of meat from cattle treated with oestradiol-17β for growth promotion purposes, according to good veterinary practice is the relevant risk, it argues that the assessment of such a risk is qualified by the difficulty in estimating the intake of such hormones. Specifically, the European Communities argues that human beings, including the populations at risk, are exposed to cumulative and synergistic effects, as they may be exposed to multiple sources of hormones and hormone residues, via several intake routes, as well as from endogenous production of some of these hormones. The European Communities contends that it is extremely difficult or impossible to assess accurately consumer exposure patterns, or other exposures from other environmental or endogenous sources, but it is also virtually impossible to assess all cumulative and synergistic effects that may arise from all potential exposure patterns, including for simultaneous exposure to several of these hormones.[569]

7.469 The European Communities argues that the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be.[570] The European Communities points out that the Opinions noted that the DNA-damaging effects of oestrogen indicate that no threshold exists for the risk from oestrogen metabolites. The Opinions concluded that, in light of the recent data on the formation of genotoxic metabolites of oestradiol, suggesting that 17β-oestradiol acts as complete carcinogen by exerting tumour initiating and promoting effects, it has to be concluded that no quantitative estimate of risk related to residues in meat could be presented.[571]

7.470 The European Communities goes on to say that the risk resulting from human consumption of meat from cattle treated with oestradiol-17β for growth promotion purposes, according to good veterinary practice, is "assessed in the real world" where "people live, work and die", or may be suffering from clinical disorders, or may be particularly vulnerable segments of the population (*e.g.*,

[566] Canada's first written submission, paras. 88-100.
[567] EC's second written submission, para.116; EC's reply to Panel question 24 after the first substantive meeting, Annex B-1.
[568] EC's second written submission, para. 116.
[569] EC's replies to Panel questions after the first substantive meeting, Annex B-1, paras. 92-96.
[570] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 94.
[571] EC's replies to Panel questions after the second substantive meeting, Annex C-1, para. 38.

like prepubertal children), etc.[572] The European Communities asserts that it considered in its assessment the potential risks resulting from the actual residues from non-treated as well as treated animals for growth promotion, and came to the conclusion that under realistic conditions of use such residues from treated animals for growth promotion do pose a higher risk and that it could not achieve the level of protection it has considered appropriate in its territory.[573]

7.471 The European Communities argues that it is not necessary to compare the two situations and then try to quantify how much one is more risky than the other and to what measurable level the risk is likely to occur, but rather to assess a situation of additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings.[574]

7.472 The European Communities contends that evidence from both the health risk associated with the use of hormones generally and the administration of hormones in animals for growth promotion purposes, is relevant for the performance of a risk assessment in the sense of the *SPS Agreement*, because both sources of evidence impact upon and inform each other.[575]

7.473 The European Communities notes that it is scientifically undisputed that life-time exposure of humans to the levels of endogenous production of oestrogen (and in particular to oestradiol-17β and its metabolites) is sufficient to cause and/or promote cancer in some individuals. This is frequently called risk of cancer from background (endogenous) exposure. This kind of exposure (and the attentive risk of cancer) cannot be avoided. The European Communities also notes that humans are exposed daily to variable levels of residues of oestradiol-17β from many exogenous sources where these hormones naturally occur, which likewise cannot be avoided.[576]

7.474 The European Communities argues that "additive risk" refers to exposure which is "further added on humans from the levels of residues in meat from animals treated with these hormones for growth promotion." Such exposure leads to a risk of cancer which is "added" to the cancer risk from the existing endogenous exposure through the background levels of hormones and through the exposure to exogenous sources, such as non-treated natural food. The European Communities cites to the 2002 US Report on Carcinogenesis and argues that it agrees with the conclusions in the SCVPH Opinions that "veterinary use of steroidal estrogens to promote growth and treat illness can increase estrogens in tissues of food-producing animals to above their normal levels", in general substantially higher than the normal (endogenously produced) levels. The European Communities argues that exposure to residues from hormone-treated meat is avoidable because these hormones are chemical substances that are deliberately added to meat.[577]

7.475 The European Communities states in response to the Panel's questions on additive risk:

> "The risk of cancer from the consumption of residues in hormone-treated meat are 'additive' (to risk of cancer from the two other sources of exposure), irrespective of whether these hormones are genotoxic carcinogens or only promote cancer through receptor-mediated mechanisms. Indeed, if they cause cancer by direct genotoxic action, the addition of such exposure increases the likelihood of the adverse effect to occur. If they act only through receptor-mediated mechanism, the risk from such exposure will be again 'additive', when they cause the presumed threshold to be

[572] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 96
[573] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 151.
[574] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para.151.
[575] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 254.
[576] EC's replies to Panel questions after the second substantive meeting, Annex C-1, paras. 48-49.
[577] EC's replies to Panel questions after the second substantive meeting, Annex C-1, para. 50.

> exceeded. The risk assessment of the European Communities has established that oestradiol-17β is a proven genotoxic carcinogen and that the other two natural hormones (testosterone and progesterone) are also suspected to be genotoxic. Moreover, the risk assessment of the European Communities has also demonstrated that the ADIs recommended by JECFA for all these hormones will be exceeded under realistic conditions of use of these hormones in the US and Canada. They will also be exceeded in any case if the more recent data on the endogenous production of the natural hormones by pre-pubertal children is taken into account."[578]

Reasoning of the Panel

7.476 In *EC – Hormones*, with respect to the methodology for a risk assessment under the second definition of paragraph 4 of Annex A of the *SPS Agreement*, the panel stated that "in this dispute, a risk assessment carried out in accordance with the *SPS Agreement* should (i) *identify* the *adverse effects* on human health (if any) arising from the presence of the hormones at issue when used as growth promoters *in meat or meat products*, and (ii) if any such adverse effects exist, *evaluate* the *potential* or probability of occurrence of these effects".[579]

7.477 Although the Appellate Body did not disagree with the panel, in its report in *EC – Hormones* it noted "that the Panel's use of 'probability' as an alternative term for 'potential' creates a significant concern. The ordinary meaning of 'potential' relates to 'possibility' and is different from the ordinary meaning of 'probability'. 'Probability' implies a higher degree or a threshold of potentiality or possibility. It thus appears that here the Panel introduces a quantitative dimension to the notion of risk."[580]

7.478 In *Australia – Salmon*, the Appellate Body further elaborated on the distinction between the two standards for risk assessment contained in Annex A(4) and the need for a substantive distinction between the evaluation of "likelihood" in the first sentence and the evaluation of "potential" in the second sentence. Specifically, the Appellate Body stated:

> "[w]e note that the first type of risk assessment in paragraph 4 of Annex A is substantially different from the second type of risk assessment contained in the same paragraph. While the second requires only the evaluation of the potential for adverse effects on human or animal health, the first type of risk assessment demands an evaluation of the likelihood of entry, establishment or spread of a disease, and of the associated potential biological and economic consequences. In view of the very different language used in paragraph 4 of Annex A for the two types of risk assessment, we do not believe that it is correct to diminish the substantial differences between these two types of risk assessments ..."[581]

7.479 Therefore, the Panel considers that it is necessary to clarify what constitutes a risk assessment as defined by Annex A(4), second sentence. The Panel considers that Annex A(4) requires a Member to (a) identify the additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs at issue (if any); (b) identify any possible adverse effect on human or animal health; and (c) evaluate the potential for that adverse effect to arise from the presence of the identified additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs.

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[578] EC's replies to Panel questions EC's replies to Panel questions after the second substantive meeting, Annex C-1, para. 51.

[579] Panel Report on *EC – Hormones (Canada)*, para. 8.101; Panel Report on *EC – Hormones (US)*, para. 8.98.

[580] Appellate Body Report on *EC – Hormones*, para. 184.

[581] Appellate Body Report on *Australia – Salmon*, footnote 69.

7.480 The Panel concludes that the European Communities has satisfied the first requirement of Annex A(4) second sentence, in that it has identified the contaminant and food at issue; namely meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes. The European Communities has also identified the possible adverse effects on human or animal health, namely neurobiological, developmental, reproductive and immunological effects, as well as immunotoxicity, genotoxicity, and carcinogenicity.[582]

7.481 The Panel must now evaluate whether it has satisfied the third requirement of the definition of a risk assessment. To do so, the Panel needs to define the terms "potential" and "arise from." The Oxford English Dictionary defines potential as "[p]ossible as opposed to actual; having or showing the capacity to develop into something in the future; latent; prospective."[583] Additionally, in *EC – Hormones* the Appellate Body observed that the ordinary meaning of 'potential' relates to 'possibility'.[584] The American Heritage Dictionary defines "arise" as to come into being, originate, to result, issue or proceed.[585]

7.482 The Appellate Body's findings in both *EC – Hormones* and *Japan – Apples* inform the definition of risk assessment in Annex A(4) second sentence. The Appellate Body has found that the requirement to conduct a risk assessment is not satisfied merely by a general discussion of the disease sought to be avoided by the imposition of a sanitary of phytosanitary measure.[586]

7.483 Specifically, in *EC – Hormones* the Appellate Body concluded that a risk assessment in this instance required not a general evaluation of the carcinogenic potential of entire categories of hormones, but rather should include an examination of residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes.[587]

7.484 In *Japan – Apples* the Appellate Body clarified that a risk assessment should refer in general to the harm concerned *as well as* to the precise agent that may possibly cause the harm.[588] In a footnote, the Appellate Body explained

> "Indeed, we are of the view that, as a general matter, 'risk' cannot usually be understood only in terms of the disease or adverse effects that may result. Rather, an evaluation of risk must connect the possibility of adverse effects with an antecedent or cause. For example, the abstract reference to the 'risk of cancer' has no significance, in and of itself, under the *SPS Agreement*, but when one refers to the 'risk of cancer from smoking cigarettes', the particular risk is given content."[589]

7.485 Given the Appellate Body's guidance and the ordinary meaning of the terms "potential" and "arising from", the Panel concludes that the European Communities was required to evaluate the possibility that the identified adverse effect came into being, originated, or resulted from the presence of residues of oestradiol-17β in meat or meat products as a result of the cattle being treated with the hormone for growth promoting purposes.

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[582] 1999 Opinion, page 72, Exhibit CDA-2.

[583] *The New Shorter Oxford English Dictionary* (Thumb Index Edition, 1993), p. 2310.

[584] *(footnote original)* The dictionary meaning of "potential" is "that which is possible as opposed to actual; a possibility"; L. Brown (ed.), *The New Shorter Oxford English Dictionary on Historical Principles*, Vol. 2, p. 2310 (Clarendon Press, 1993). In contrast, "probability" refers to "degrees of likelihood; the appearance of truth, or likelihood of being realized", and "a thing judged likely to be true, to exist, or to happen"; Ibid., p. 2362.

[585] The American Heritage Dictionary of the English Language (4th ed., 2000).

[586] Appellate Body Report on *Japan – Apples*, para. 202.

[587] Appellate Body Report on *EC – Hormones*, para. 200.

[588] Appellate Body Report on *Japan – Apples*, para. 202.

[589] Appellate Body Report on *Japan – Apples*, at footnote 372.

7.486 The Panel, as noted above, will not conduct its own risk assessment or impose its own scientific opinions on the European Communities.[590] However, the Panel must make an objective assessment of whether the Opinions issued by the SCVPH satisfy the definition contained in Annex A(4) to the *SPS Agreement*.

7.487 As a preliminary matter, the Panel notes that there has been significant debate between the parties about the relevance of the Codex and JECFA definitions of the various phases of a risk assessment as well as about a risk assessment's role in the larger process of risk analysis, which consists of three components: risk assessment, risk management, and risk communication.[591]

7.488 The Panel also recalls that the European Communities argues that the broader concept of risk analysis, as defined by Codex, including the risk management phase, must be considered in evaluating whether the European Communities conducted a risk assessment within the meaning of Article 5.1 and Annex A(4).

7.489 Specifically, the European Communities points out that, as defined by Codex, risk assessment is normally considered to be only the first component of a three part process.[592] The European Communities argues that Canada makes little or no reference to the second component of risk analysis, which has to be completed *after* the completion of the four steps of risk assessment, namely risk management. The European Communities defines risk management as the process of "weighing policy alternatives in the light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures."[593] The European Communities also asserts that the Appellate Body has confirmed that a risk assessment within the meaning of Article 5.1 includes a risk management stage which is the responsibility of the regulator to carry out and not of the scientific bodies.[594]

7.490 The Panel agrees with the European Communities that the relevant definition against which to measure the EC Opinions in order to determine whether they constitute a risk assessment is the one contained in the *SPS Agreement*, namely that set forth in Annex A(4). As noted above, the Panel has found that the text of Annex A(4) second sentence defines a risk assessment as evaluating the possibility that an identified adverse effect came into being, originated, or resulted from the presence of the identified additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs.

7.491 The European Communities argues that the Appellate Body in the original *EC – Hormones* case confirmed that a risk assessment within the meaning of Article 5.1 includes a "risk management" stage which entails weighing policy alternatives in light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures. Although the Appellate Body disapproved of the original panel's distinction between "risk assessment" and "risk management" because it had no textual basis in the Agreement, this Panel can find no statement by the Appellate Body confirming that what the European Communities describes as risk management is included within the definition of a risk assessment as set forth in Annex A(4) of the *SPS Agreement*. In fact, the Appellate Body stressed that Article 5 and Annex A speak of *risk assessment* only and that the term *risk management* is not to be found either in Article 5 or in any other provision of the *SPS Agreement*.[595]

[590] See para. 7.432 above.
[591] Codex Procedural Manual, 15th ed., p. 44.
[592] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 135.
[593] EC's replies to Panel questions after the first substantive meeting, Annex B-1, paras. 136-137.
[594] EC's second written submission, para.116.
[595] Appellate Body Report on *EC – Hormones*, para. 181.

7.492 The Panel agrees with the Appellate Body that its role as a treaty interpreter is to "read and interpret the words actually used by the agreement under examination, and not words which the interpreter may feel should have been used."[596] The Panel takes note of the Appellate Body's finding that a risk assessment can take into account "matters not susceptible of quantitative analysis by the empirical or experimental laboratory methods commonly associated with the physical sciences."[597] However, the Panel finds that neither that finding nor the text of the Agreement includes within the definition of a risk assessment the concepts put forward by the European Communities as "risk management." Therefore, the Panel maintains that it must determine whether the European Communities evaluated the possibility that the identified adverse effects came into being, originated, or resulted from the presence of residues of oestradiol-17β in meat or meat products as a result of the cattle being treated with the hormone for growth promotion purposes. To that end, the Panel requested the opinions of the scientific experts on what, exactly, the European Communities evaluated in its Opinions.

7.493 The Panel specifically asked the experts whether the EC Opinions identified the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol-17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice and to what extent the Opinions evaluated the potential occurrence of these adverse effects.[598]

7.494 Dr. Boobis concluded that "the EC has not identified the potential for adverse effects on human health of residues of oestradiol found in meat from treated cattle. This is because the analysis undertaken was focused primarily on hazard identification. There was little in the way of hazard characterization, and no independent exposure assessment was undertaken.[599]

7.495 Dr. Guttenplan concluded that the European Communities had done a thorough job in identifying the potential for adverse effects on human health of oestradiol-17β found in meat derived from cattle to which this hormone had been administered. Specifically, Dr. Guttenplan found that the European Communities had identified a number of potential adverse effects, established metabolic pathways relevant to these effects, and examined mechanisms of these effects. In addition it had performed thorough studies of residue levels in cattle, and the environment. Dr. Guttenplan also concluded that the evidence evaluating the occurrence of adverse effects is weak. He found that the animal models were very limited and the target organs do not coincide well with the target organs in humans. He also pointed out that there are "basically no epidemiological studies comparing matched populations consuming meat from untreated and hormone-treated cattle. Thus, little can be inferred about the potential occurrence of the adverse effects, the potential for adverse effects seems reasonable."[600]

7.496 Dr. Boisseau noted that "in the 1999 report, SCVPH concluded also that '... it is clear that exogenous oestrogens, present in oral contraceptives or used in hormonal replacement therapy in women, are responsible for an increase of endometrial cancer and, to lesser extent, some increased risk of breast cancer, [but] there is no direct evidence on the consequences of the contribution of exogenous oestradiol-17β originating from the consumption of treated meat'."[601]

7.497 Dr. Cogliano observed that even though the European Communities does demonstrate through scientific evidence that oestradiol-17β is genotoxic, the issue is whether this genotoxicity

[596] Appellate Body Report on *EC – Hormones*, para. 181.
[597] Appellate Body Report on *EC – Hormones*, para. 187.
[598] Panel question 13 to the scientific experts, Annex D, p. 22.
[599] Replies by the scientific experts to Panel questions, Annex D, para. 144.
[600] Replies by the scientific experts to Panel question 13, Annex D, para. 145.
[601] Replies by the scientific experts to Panel questions, Annex D, para. 132.

would occur at levels found in meat residues. In that respect, Dr. Cogliano concluded that the European Communities has not established that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans.[602]

7.498 The Panel specifically asked the experts whether the European Communities had demonstrated that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth promotion purposes. Dr. Boisseau concluded that the European Communities did not demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth promotion purposes. Additionally, Dr. Boisseau stated that the kind of evidence required to demonstrate such potential adverse effects should be (a) toxicological data indicating that the values of the ADIs established by JECFA are not conservative enough, and (b) data on residues in treated/non-treated cattle and on daily production of hormones in sensitive individuals[603] indicating that the hormonal residue intake associated with the consumption of meat from treated cattle is such that the established ADIs would be exceeded in the case of use of growth promoters.[604]

7.499 Dr. Boobis stated that, in his view, none of the information provided by the European Communities demonstrates the potential for adverse effects in humans of any of the six hormones in meat from cattle in which they are used for growth promotion purposes at the levels to which those consuming such meat would be exposed. The studies on genotoxicity provide no convincing evidence of potential for harm in consumers. The carcinogenic effects observed are entirely consistent with a hormonal mode of action that exhibits a threshold that would be well above the intake arising from consumption of meat from treated cattle.[605]

7.500 Dr. Guttenplan found that the levels in meat could result in bioavailable oestrogen exceeding the daily production rate of oestradiol in pre-pubertal children. "For pre-pubertal children, even with the low bioavailabilty of estrogen ... and its low levels in meats, it appears possible that intake levels would be within an order of magnitude of those of the daily production rate. This is greater than FDA's ADI and suggests some risk to this population. If there [are] genotoxic effects of estradiol in children, they may be reflected over a lifetime, as mutations arising from DNA damage are permanent. It seems the more accurate methods of analysis could now be used to measure the effect of eating hormone-treated beef on blood levels of estrogen in children and post-menopausal women. If practical, this experiment would be important in establishing or refuting the arguments of the EC."[606]

7.501 To the extent that the European Communities argues that the relevant risk from hormones is an "additive risk" the experts concluded that the European Communities did not assess the extent to which residues of growth promoting hormones in meat contribute to additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings.[607]

7.502 Dr. Cogliano explains that even if the fact that a substance is a carcinogenic hazard led an agency to make a decision on the qualitative element alone, many agencies still prefer to examine the exposure in their country to determine what to do.[608] Indeed Dr. Boobis indicates that stopping the

[602] Replies by the scientific experts to Panel questions, Annex D, para. 180.
[603] Such as prepubertal children.
[604] Replies by the scientific experts to Panel questions, Annex D, para. 406.
[605] Replies by the scientific experts to Panel questions, Annex D, para. 408.
[606] Replies by the scientific experts to Panel question 52, Annex D, para. 413.
[607] Replies by the scientific experts to Panel question 56, Annex D, paras. 422-431.
[608] Transcript of the Panel meeting with the experts, Annex G, para. 438.

risk assessment once it was identified that the hazard was such that the dose response was going to be linear, i.e. there is no threshold, would be an unusual circumstance. He states that in most circumstances one would want to understand the relationship between the hazard and the level of exposure that was occurring. For that reason one would progress at least to a semi-quantitative evaluation of the exposure and risk, rather than just stopping at a simple identification of hazard.[609]

7.503 Finally, the Panel has looked at the Opinions and found statements that indicate that specific studies on the potential for the adverse health effects identified by the European Communities to arise from consumption of meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes were not conducted.

7.504 The 1999 Opinion looked at three main areas of potential adverse effects: developmental effects on different stages of life; the relationship between oestrogens and cancer; and the effect of sex hormones on the immune system. In each of these areas, little or no data was presented directly that any of the potential adverse health effects identified come into being, originate, or result from the consumption of meat and meat products which contain veterinary residues of oestradiol-17β as a result of the cattle being treated with the hormone for growth promoting purposes.

7.505 With respect to the developmental effects of exogenous sex hormones, the 1999 Opinion recites generally the biological functions of sex hormones in the biological development of a human being and cites to studies that involve the application of diethylstilbestrol (DES) in experimental settings, even though DES is not one of the possible sources of oestradiol-17β residues in meat from treated cattle.[610] With respect to prepubertal children, the 1999 Opinion again cites studies having to do with DES as well as testosterone and allylestrenol (a steroid used in prevention of spontaneous abortion).[611] Although the developmental effects of oestrogens are discussed generally, including some potential adverse health effects, there is no examination of whether these effects arise from the presence of residues of oestradiol-17β in meat and meat products as a result of the cattle being treated with the hormone for growth promotion purposes. In fact, the 1999 Opinion states that "the information available so far falls short of the ideal, or even the sufficient standard to allow observers a well informed judgment when assessing exposure regarding what is acceptable from what is not."[612]

7.506 Regarding cancer, the 1999 Opinion states that "no study has assessed the effects of hormones as growth promoters in farm animals on cancer occurrence in humans. Arguments to be considered when evaluating the hypothesis of a potential link between the use of food promoters in farm animals and cancer in humans come both from descriptive epidemiology, including studies in migrants, and etiologic epidemiology on diet and cancer as well as on hormones and cancer."[613] "Currently one cannot confirm nor refute the association between high rates of breast cancer and high hormone-treated meat consumption in North-America. This should be urgently studied."[614] Additionally, the 1999 Opinion noted that:

> "The difficulty of evaluating health effects at low dose is here compounded by the fact that the data on exposures of human populations are exceedingly limited. No large data are available on representative samples of foods collected in countries allowing or banning growth promoters in farm animals. Most often, published levels concern measurements realized by the producers of the substances themselves under experimental conditions. However, data on the concentration of hormones and their

[609] Transcript of the Panel meeting with the experts, Annex G, para. 442.
[610] 1999 Opinion, pp. 5-16.
[611] 1999 Opinion, p. 13.
[612] 1999 Opinion, p. 6.
[613] 1999 Opinion, p. 16.
[614] Ibid.

> metabolites present in edible tissues of treated animals are lacking. In addition, the methods used for measurements require a critical reappraisal. Data on the nature and amount of metabolites produced by the target animal are missing."[615]

7.507 Finally, in examining the effect of sex hormones on the immune system, the 1999 Opinion states that "no sound epidemiological data are currently available to establish a link between nutrition, especially meat consumption, and the occurrence of (and apparent current increase in) autoimmune diseases."[616] Additionally, the 1999 Opinion found that relevant data

> "indicate that oestrogens modulate the immune system in many species. Direct human data at near physiological levels of oestradiol are lacking. Vingerhoets et. al., (1998) have conducted a self-reporting questionnaire study of DES daughters. A statistically significant difference in the incidence of infections was identified compared with control. This may be considered to be linked to imprinting by DES in utero.
>
> In conclusion, at relatively high doses oestradiol does produce a number of adverse effects on the immune system in humans, e.g. allergy to topical oestradiol (Boehnke and Gall, 1996). The above findings while indicating a possible concern are insufficient to identify whether immune effects could occur in consumers from the ingestion of meat or meat products containing oestradiol residues."[617]

7.508 The 1999 Opinion cited a new method for determining blood levels of oestradiol which suggested that the levels were 100 fold lower than previously determined and the metabolic clearance rate too high by a factor of 10. The 1999 Opinion concluded that if these methods were correct the acceptable daily intake established by the US Food and Drug Administration for meat and meat products derived from treated cattle would be at least 85 fold and possibly as much as 1,700 fold too high. However, the 1999 Opinion went on to note that "[g]iven all of the uncertainties in these estimates, it appears that the data are insufficient to form the basis of a sound risk assessment."[618]

7.509 All of the statements of the experts, and indeed statements from the Opinions, indicate that the European Communities has evaluated the potential for the identified adverse effects to be associated with oestrogens in general, but has not provided analysis of the potential for these effects to arise from consumption of meat and meat products which contain residues of oestradiol-17β as a result of the cattle they are derived from being treated with the hormone for growth promotion purposes. The Panel, therefore, concludes that although the European Communities has evaluated the association between excess hormones and neurobiological, developmental, reproductive and immunological effects, as well as immunotoxicity, genotoxicity, and carcinogenicity, it has not satisfied the requirements of the definition of a risk assessment contained in Annex A(4) because it has not evaluated specifically the possibility that these adverse effects come into being, originate, or result from the consumption of meat or meat products which contain veterinary residues of oestradiol-17β as a result of the cattle being treated with the hormone for growth promotion purposes.

[615] Ibid., p. 20
[616] 1999 Opinion, pp. 22-23.
[617] 1999 Opinion, p. 45.
[618] 1999 Opinion, pp. 38-39.

Does the science support the conclusions of the Opinions?

Introduction

7.510 The Panel agrees with the reasoning of the Panel in *Japan – Apples (Article 21.5 – US)* that "the scientific evidence which is being evaluated must support the conclusions of the [risk assessment]. Therefore, if the conclusions of the risk assessment are not sufficiently supported by the scientific evidence referred to in the [risk assessment], then there cannot be a risk assessment appropriate to the circumstances, within the meaning of Article 5.1".[619] Although the Panel has already found, above, that the Opinions do not satisfy the definition of a risk assessment in Annex A(4) of the *SPS Agreement*, the Panel wishes to ensure that it has conducted a complete and objective assessment of the facts. Therefore, in determining whether the European Communities complied with Article 5.1, the Panel will determine whether the scientific evidence referred to in the Opinions supports the conclusions contained therein.

Summary of the main arguments of the parties[620]

7.511 **Canada** recalls that the most important conclusion of the SCVPH relied upon by the European Communities to justify its continued ban on oestradiol-17β as a growth promoter is that this hormone is genotoxic. According to Canada, the problem with the SCVPH's conclusion about genotoxicity is that it is not supported by the evidence. This can be demonstrated with reference to the SCVPH's own opinions. It can be demonstrated with reference to the work of other international scientific authorities. And it can be demonstrated with reference to the European Communities' own conclusions.

7.512 First, Canada argues, the SCVPH itself acknowledges that its conclusion about the genotoxicity of oestradiol-17β is simply a hypothesis, based on a limited set of studies done either in vitro or on laboratory specimens under unrealistic conditions. The hypothesis is that one single reactive metabolite can damage DNA and lead to tumour initiation. It is on the basis of this conclusion that the SCVPH concludes that a threshold does not exist for carcinogenic effects arising from exposure to oestradiol-17β and its metabolites.

7.513 Canada considers that the EC hypothesis completely disregards established scientific evidence that mechanisms exist within the human body to control the formation of potentially genotoxic metabolites in vivo and to eliminate DNA adducts that may be formed. The Opinions make only passing reference to "inactivating processes", but then go on to assume that these inactivating processes are insufficient in the case of catechol oestrogens.[621] This conclusion is surprising in the light of the SCVPH's own acknowledgement that "[n]o data are currently available on the genotoxic effects of exogenous low-dose oestrogens." As a result, the SCVPH conclusions about the potential occurrence of tumours as a result of the genotoxicity of oestradiol-17β, on which the European Communities relies, amounts to no more than the identification of theoretical risk.

7.514 According to Canada, other scientific and regulatory authorities have all indicated that the SCVPH's conclusion on the genotoxicity of oestradiol-17β is more theory than reality. For example, in its replies to the Panel's questions, the European Communities cites numerous times a 2000 report by JECFA in which JECFA acknowledges the "genotoxic potential" of oestradiol-17β. However, what the European Communities fails to indicate is that in the same report, JECFA also stated that it

[619] Panel Report on *Japan – Apples (Article 21.5 – US)*, para. 8.136 (original footnote omitted).

[620] A more detailed account of the parties' arguments can be found in the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[621] 1999 Opinion, p. 72, Exhibit CDA-2.

was "not certain that this pathway is relevant in vivo at physiological concentrations of estradiol." In the end, JECFA concluded that "the carcinogenicity of estradiol-17β is most probably a result of its interaction with hormonal receptors." In the light of its conclusion that receptor-based carcinogenicity is dose-dependent, JECFA identified a threshold level and established an ADI.

7.515 Canada adds that, after reviewing the evidence related to the genotoxicity of oestradiol-17β, the Committee for Veterinary Medicinal Products (CVMP) of the European Medicines Agency came to a similar conclusion in a 1999 report. It found that new studies confirmed the earlier findings and clearly indicated that hormones and/or their synthetic analogues were not associated with genotoxic properties.

7.516 Finally, Canada notes that when considering exposure to oestradiol-17β when used as a growth promoter, the European Communities is categorical about the risks arising from one single reactive oestradiol metabolite and hence concludes that to achieve its appropriate level of protection it must not allow exposure to even one molecule. However, even though the European Communities expresses significant concern about the risks from oestradiol-17β metabolites from meat from treated animals, the European Communities appears not to find it necessary to even provide health advisories about the potential risks from other sources.[622]

7.517 The **European Communities** argues that it is important to understand that the issue of the dose administered is not relevant for the *in vivo* genotoxicity in the case of oestradiol-17β. The European Communities goes on to note that it appears that the doses used to elicit *in vivo* mutagenicity[623] are not massively high, but rather that they seem to fall within the safety margin established by JECFA, which means that the residues in meat from hormone-treated cattle are also capable of producing this adverse effect.[624]

7.518 The European Communities argues that the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be.[625] The European Communities goes on to say that the risk resulting from human consumption of meat from cattle treated with oestradiol-17β for growth promotion purposes, according to good veterinary practice, is "assessed in the real world" where "people live, work and die", or may be suffering from clinical disorders, or may be particularly vulnerable segments of the population (e.g., like prepubertal children), etc.[626]

7.519 The European Communities notes that it is scientifically undisputed that life-time exposure of human to the levels of endogenous production of oestrogen (and in particular to oestradiol-17β and its metabolites) are sufficient to cause and/or promote cancer in some individuals. This is frequently called risk of cancer from background (endogenous) exposure. This kind of exposure (and the attentive risk of cancer) cannot be avoided. The European Communities also notes that humans are exposed daily to variable levels of residues of oestradiol-17β from many exogenous sources where these hormones naturally occur, which likewise cannot be avoided.[627]

[622] Canada's second written submission, paras. 86-98.
[623] Ability of a physical, chemical, or biological agent to induce heritable changes (mutations) in the genetic material in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof) (replies of Dr. Boobis and Dr. Guttenplan to Panel question 2 to the experts. Annex D, paras. 34 and 55).
[624] EC's replies to Panel questions after the second substantive meeting, Annex C-1, para. 23.
[625] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 94.
[626] EC's replies to Panel questions after the first substantive meeting, Annex B-1, paras. 94 and 96.
[627] EC's replies to Panel questions after the second substantive meeting, Annex C-1, paras. 48-49.

Reasoning of the Panel

7.520 The Panel's task is to determine whether the scientific evidence supports the conclusions in the Opinions. The Panel notes in this respect that the 1999 Opinion concluded that "for oestradiol genotoxicity has already been demonstrated explicitly."[628] The 1999 Opinion also concluded that oestradiol-17β is a complete carcinogen that exhibits tumour initiating and tumour promoting effects.[629] Finally, the 1999 Opinion found that "any excess exposure towards 17β-oestradiol and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the population which have been identified as particularly sensitive, such as prepubertal children.[630] In the 2000 and 2002 Opinions, the SCVPH concluded that none of the additional science developed in the intervening years justified changing those conclusions.

7.521 The Panel is not in a position to evaluate the scientific data the SCVPH reviewed in drawing its conclusions. For this reason, the Panel consulted a group of scientific experts and asked them to evaluate the EC Opinions as well as the underlying science.

7.522 The European Communities urged the Panel to disregard the responses of two particular experts because their positions are "purely theoretical" and for the additional reason that they have "never done any specific research on these hormones nor have they published something on these substances."[631] In that vein, the European Communities cites to the Appellate Body's rejection of an opinion given by a scientist in the original *EC – Hormones* dispute in 1998 because it did not "purport to be the result of scientific studies carried out by him or under his supervision focusing specifically on residues of hormones in meat from cattle fattened with such hormones ..."[632] However, the Panel finds that Appellate Body in its report on *EC – Hormones* spoke to a different issue. In that instance the scientist was making specific estimates about the likelihood of breast cancer being caused by eating meat containing oestrogens, even though the scientist had not studied the matter.

7.523 In this case, the Panel has asked the experts not to make their own scientific conclusions but to evaluate the Opinions as experts in the conducting of risk assessments on food additives and contaminants and to assist the Panel in determining whether the evidence relied upon by the SCVPH supports the conclusions in its Opinions. To that end the Panel found the comments by all the experts helpful in its analysis and none shall be disregarded

7.524 In response to specific questions from the Panel, the experts provided the following information.

7.525 With respect to the genotoxicity of oestradiol-17β, Dr. Boisseau explained that JECFA's conclusion that oestradiol-17β had genotoxic potential was based on the general agreement that oestradiol-17β is associated with a genotoxic effect, thus

> "... although it recognized that oestradiol-17β does not lead to positive results in all the classical tests which have been used to demonstrate its genotoxicity and its mutagenicity (oestradiol-17β did not cause gene mutations *in vitro* and gives, in some assays, sporadic but unconfirmed positive results), JECFA, in its fifty second session held in 1999 concluded 'that oestradiol-17β has genotoxic potential.'"[633]

[628] 1999 Opinion, p. 75, Exhibit CDA-2.
[629] 1999 Opinion, p. 73.
[630] 1999 Opinion, p. 71.
[631] EC's comments on experts replies to Panel questions, Annex F-1, pp. 35-36.
[632] EC's comments on experts replies to Panel questions, Annex F-1, p. 14 citing Appellate Body Report on *EC – Hormones*, para. 198.
[633] Replies by the scientific experts to Panel questions, Annex D, paras. 134-135.

7.526 In evaluating the EC assertion that the fact that doses of oestradiol-17β used in growth promotion are low is irrelevant because there is no threshold for substances which have genotoxic potential, Dr. Boisseau stated that the general principle did not apply to naturally occurring hormones, which are produced by both humans and food producing animals. Dr. Boisseau noted that even in the absence of any consumption of food coming from animals treated by growth promoting hormones, humans are naturally and continuously exposed to these natural hormones through, among others, (a) their own production of these hormones which may be very high, for example in the case of pregnant women, (b) the consumption of meat from non treated cattle, (c) the consumption of meat from other food producing animals, (d) the consumption of milk and eggs. There is no epidemiological survey indicating that this continuous exposure of humans to these natural hormones results in any identified risk for health.[634]

7.527 Dr. Cogliano explained that "the EC's statement that a threshold cannot be identified reflects their view of genotoxic mechanisms, just as the contrary statement that there is a threshold and that this threshold is above the levels found in meat residues reflects how Canada and the US view genotoxic mechanisms. Neither statement has been demonstrated by the scientific evidence, rather, they are different assumptions that each party uses in their interpretation of the available evidence."[635]

7.528 Dr. Guttenplan replied that

> "[T]he data referred to by the EC supports a genotoxic mechanism as well as a hormonal mechanism. It is true that there is no reason to expect a threshold to exist for a genotoxic chemical. Although DNA repair can occur, it presumably is occurring at all doses and the fraction of DNA damage repaired probably does not change at physiological levels, because the repair enzymes are unlikely to be saturated. The statement that, 'the fact that doses used in growth promotion are low is not of relevance' is not necessarily true. (para. 118-119 of EC Rebuttal Submission (US case)). For any toxin the dose determines the risk. When exposure is very low risk will be very low. However, one can argue about the definition of 'low'. It should also be noted that at very low levels of genotoxic carcinogens the decrease in risk is more than proportional than the decrease in applied dose."[636]

7.529 Dr. Cogliano stated in his written responses that the identification of oestradiol-17β as a human carcinogen indicates that there are potential adverse effects on human health when oestrodiol-17β is consumed in meat from cattle treated with hormones for growth promotion purposes.[637] At the meeting with the Panel, Dr. Cogliano clarified that the IARC has classified oestradiol-17β as possibly carcinogenic based on sufficient evidence in experimental animals. The agents that are known to be carcinogenic in humans are the steroidal oestrogens, non-steroidal oestrogens, and various oestrogen-progestin combinations as used either as birth-control pills or menopausal therapy.[638]

7.530 Dr. Boobis concluded that there is no good evidence that oestradiol is genotoxic *in vivo* or that it causes cancer by a genotoxic mechanism. Indeed the evidence is against this. Hence, the scientific evidence does not support the European Communities' position that the levels of the hormones in meat from treated cattle are not of relevance.[639]

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[634] Replies by the scientific experts to Panel questions, Annex D, para. 182.
[635] Replies by the scientific experts to Panel questions, Annex D, para. 186.
[636] Replies by the scientific experts to Panel questions, Annex D, para. 187.
[637] Replies by the scientific experts to Panel questions, Annex D, para. 154.
[638] Transcript of the Panel meeting with the experts, Annex G, para. 327.
[639] Replies by the scientific experts to Panel questions, Annex D, para. 184.

7.531 In a review of the scientific literature and the 1999 report of the Committee for Veterinary Medicinal Products of the European Medicine Agency, Dr. Boisseau concluded that the demonstration remains to be made that the observed indicator effects are representative of mutagenesis at the gene or chromosome level and also occur in somatic cells *in vivo*. This is not likely in the view of the following: earlier studies had mostly indicated that hormones do not induce micronuclei or other chromosomes aberration types *in vivo*. With the exception of the study reported by Dhillon and Dhillon, the recent data confirm the earlier findings and clearly indicate that hormones and/or their synthetic analogues are not associated with genotoxicity properties in the bone marrow micronucleas assay *in vivo*.[640]

7.532 With respect to the carcinogenic and tumour promoting qualities of oestradiol-17β, Dr. Boisseau noted that if the SCVPH, in the 1999 Opinion, expresses its concern in concluding that "[f]inally, in consideration of the recent data on the formation of genotoxic metabolites of oestradiol suggesting oestradiol-17β acts as complete carcinogen by exerting tumour initiating and promoting effects ... no quantitative estimate of the risk related to residues in meat could be presented," it provides no data indicating that oestradiol-17β is associated with the increase of tumours in tissues or organs which are not hormone dependent.[641] Dr. Boisseau concludes that "the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans."[642]

7.533 In addition, Dr. Boisseau concluded that the scientific evidence relied upon in the Opinions does not support the conclusion that carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity.[643]

7.534 Dr. Boobis also pointed out that the evidence is against direct modification of DNA *in vivo* by hormones in meat from treated animals, or by their metabolites produced *in vivo*. Indirect modification could conceivably come about by products of active oxygen. The DNA repair[644] processes for this are amongst the most efficient (*Arai et al, 2006; Russo et al, 2004)* and even if such modification did occur, it is anticipated that no heritable change would result, because of DNA repair (*Arai et al, 2006)*. This would be true even at the levels of exposure that could arise should GVP not be followed.[645]

7.535 Dr. Boisseau also expressed his opinion that epidemiological studies carried out in humans during long enough to take into account this "long latency period" will not be able to discriminate, in the case of a possible but limited increase of tumours, between the responsibilities of (a) hormone residues resulting from the treatment of food producing animals by growth promoting hormones, (b) hormone residues resulting from the endogenous production of these animals, and (c) other components of the diet including other food additives and contaminants. That is the reason for which, to his knowledge, even though the hormones in dispute have already been used as growth promoters over a significant number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters.[646]

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[640] Replies by the scientific experts to Panel questions, Annex D, para. 136.
[641] Replies by the scientific experts to Panel questions, Annex D, para. 141.
[642] Replies by the scientific experts to Panel questions, Annex D, para. 142.
[643] Replies by the scientific experts to Panel questions, Annex D, para. 156.
[644] DNA repair mechanisms refer to the ability of an organism to recognize different types of damage to DNA and repair it (replies of Dr. Boobis and Dr. Guttenplan to Panel question 22 to the experts, Annex D, paras. 201 and 204).
[645] Replies by the scientific experts to Panel questions, Annex D, para. 202.
[646] Replies by the scientific experts to Panel questions, Annex D, para. 209.

7.536 In response to the citation by the European Communities of data indicating different cancer rates between the United States and Europe, Dr. Boobis stated that there is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans. Dr. Boobis acknowledged that an appreciable number of studies show an association between a risk of certain cancer types and the consumption of meat, however he pointed out that the studies show little relationship with whether the meat is from animals treated with growth promoting hormones or not. Dr. Cogliano noted that although it is possible that differences in exposure to exogenous hormones could be one cause of the different breast cancer rates in the United States and the European Communities, the data are not sufficiently specific to establish a link. Dr. Guttenplan also concluded that the epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters.[647]

7.537 Additionally, in response to direct questioning during the Panel meeting with the experts, Drs. Boobis, Boisseau, and Guttenplan all agreed that there is no appreciable risk of cancer from residues of oestradiol-17β in meat and meat products from cattle treated with the hormone for growth promotion purposes. While all the experts who responded to the question agreed that a zero risk could not be guaranteed, the actual level of risk was in their view so small as to not be calculable.[648]

7.538 Finally, the Opinions themselves contain statements that indicate that the science does not support the conclusions in the Opinions. The 1999 Opinion considered that the link, if any, between cancer and consumption of hormone-treated meat cannot, at present, be confirmed nor refuted.[649] It is also important to note that the only study cited with respect to cancer in susceptible populations, such as foetuses and prepubertal children, has to do with *in utero* exposure to DES, which is banned in Canada and is not the source of the oestradiol-17β residues in the meat and meat products that are the subject of the European Communities' ban.[650]

7.539 With respect to the other potential adverse effects identified by the European Communities, the 1999 Opinion also concludes that no sound epidemiological data are currently available to establish a link between nutrition, especially meat consumption, and the occurrence of (and apparent current increase in) autoimmune diseases.[651] As to the developmental effects of exogenous sex hormones on puberty in humans, the 1999 Opinion noted that although precocious puberty is somewhat common in the United States, "the importance of environmental oestrogenic compounds present in plastics, insecticides, and *meat from animals treated with sex hormones*, while suggestive, remains as only a possibility in affecting an early onset of puberty."[652]

7.540 The Panel has evaluated the evidence. The Panel considered the SCVPH's own characterization of the science in the Opinions as well as the replies of the experts to the Panel's questions, the transcript of the experts meeting with the Panel, and the submissions of the parties. The Panel found that the views expressed by the experts who answered the questions, provided clear and consistent answers, and who had particular expertise in the relevant areas being discussed, were consistent with the statements in the Opinions cited above. The Panel's evaluation of the expert views and the plain language of the Opinions themselves leads the Panel to conclude that the scientific evidence referred to in the Opinions does not support the European Communities' conclusion that for oestradiol-17β genotoxicity had already been demonstrated explicitly[653], nor does it support the

[647] Replies by the scientific experts to Panel questions, Annex D, paras. 224, 230, 231, 238, 239, 241 and 242.
[648] Transcript of the Panel meeting with the experts, Annex G, paras. 704-742
[649] 1999 Opinion, pp. 17-18.
[650] 1999 Opinion, p. 21.
[651] 1999 Opinion, pp. 22-23.
[652] 1999 Opinion, p. 14. (emphasis added).
[653] 1999 Opinion, p. 75.

conclusion that the presence of residues of oestradiol-17β in meat and meat products as a result of the cattle being treated with the hormone for growth promotion purposes leads to increased cancer risk. Additionally, the scientific evidence does not support the European Communities' conclusions about the adverse immunological and developmental effects of consuming meat and meat products from cattle treated with oestradiol-17β for growth promotion purposes. Therefore, the Panel is of the view that the scientific evidence referred to in the Opinions does not support the conclusions reached by the European Communities.

Conclusion

7.541 On the basis of the above, the Panel concludes that, in its Opinions, the European Communities took into account risk assessment techniques of the relevant international organizations. The Panel nonetheless concludes that the European Communities has not satisfied the requirements of the definition of a risk assessment contained in Annex A(4) of the *SPS Agreement* and the scientific evidence evaluated does not support the conclusions in the risk assessment. The Panel concludes that the European Communities has not conducted a risk assessment as appropriate to the circumstances within the meaning of Article 5.1 of the *SPS Agreement*.

(iii) Is the measure "based on" a risk assessment

Introduction

7.542 The second question to address when determining whether an SPS measure is consistent with Article 5.1 is whether that measure is "based on" a risk assessment. For an SPS measure to be based on a risk assessment, there must be a rational relationship between the measure and the risk assessment.[654]

7.543 Specifically, the Appellate Body in *EC – Hormones* explained that "Article 5.1, when contextually read as it should be, in conjunction with and as informed by Article 2.2 of the *SPS Agreement*, requires that the results of the risk assessment must sufficiently warrant -- that is to say, reasonably support -- the SPS measure at stake."[655] The Appellate Body went on to explain that this requirement is a substantive one.[656]

Summary of the main arguments of the parties[657]

7.544 **Canada** argues that, even if the Opinions are considered to constitute a risk assessment, the EC measure is not "based on" that risk assessment.

7.545 According to Canada, all that the SCVPH has arguably identified are some potential adverse effects associated with oestradiol-17β *per se*. It has not demonstrated that these adverse effects occur as a result of consumption of the quantity of oestradiol-17β in meat derived from treated farm animals.[658]

7.546 Therefore, in Canada's view, even if the conclusions of the Opinions on the adverse effects of oestradiol-17β are correct, the rational response would be for the European Communities to ban oestradiol-17β, or at least to inform consumers of the various sources of oestradiol-17β and the

[654] Appellate Body Report on *EC – Hormones*, para. 193.
[655] Appellate Body Report on *EC – Hormones*, paras. 193-194.
[656] Ibid.
[657] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.
[658] Canada's first written submission, paras. 101-108.

actions they should take to minimize exposure. It has instead chosen to respond to advice about the potential adverse effects of oestradiol-17β from all sources by banning only meat from animals treated with oestradiol-17β for certain purposes. As a result, the conclusions of the Opinions do not support the conclusions underlying the measure, so the measure is not "based on" a risk assessment.

7.547 The **European Communities** replies that, in arguing that the ban on oestradiol-17β is not based on a risk assessment, Canada essentially repeats its arguments on the lack of specificity of the risk assessment. The European Communities argues in this respect that it has identified the adverse effects of oestradiol-17β and that it has evaluated their potential occurrence.[659]

Reasoning of the Panel

7.548 The Panel has concluded that the Opinions do not constitute a risk assessment because the Opinions do not satisfy the definition of a risk assessment contained in Annex A(4) second sentence and because the scientific evidence referred to in the Opinions does not support the conclusions therein. Because the Opinions are not a risk assessment as appropriate to the circumstances, the measure cannot be based on a risk assessment within the meaning of Article 5.1.[660]

(iv) Conclusion

7.549 In light of the above, the Panel concludes that the EC implementing measure on oestradiol-17β is not compatible with Article 5.1 of the *SPS Agreement*.

(f) Compatibility of the EC implementing measure with Article 5.7 of the *SPS Agreement*

(i) Introduction

7.550 We have already concluded that the EC implementing measure does not comply with the provisions of Article 5.1 of the *SPS Agreement*. To the extent that we are not seeking to determine any level of nullification or impairment, but rather whether the European Communities has removed the measure found to be inconsistent with a covered agreement in the *EC – Hormones* dispute, we could conclude at this stage that, by adopting Directive 2003/74/EC, the European Communities has not – fully – removed the measure found to be inconsistent with the *SPS Agreement*. We recall, however, the purpose of our considering the EC claims of violation of Article 23.1 of the DSU, read together with Article 22.8 and Article 3.7 of the DSU. It is to assist the DSB in achieving a satisfactory settlement of the matter in accordance with the rights and obligations under the DSU and under the covered agreements, and to allow the Appellate Body to make findings as may be necessary should it disagree with our findings in relation to Article 23.1 and 23.2(a) of the DSU. We therefore proceed with a review of the conformity of the EC measure with Article 5.7 of the *SPS Agreement*.

(ii) Summary of the main arguments of the parties[661]

7.551 The **European Communities** argues that Directive 2003/74/EC provides that the use of five of the six hormones at issue is provisionally forbidden. This ban is based on a comprehensive risk assessment and, thus, is fully compliant with the DSB recommendations and rulings. In particular, as stipulated by the Appellate Body, the results of the risk assessment provide the "available pertinent

[659] EC's second written submission, para. 128.

[660] Panel Report on *Japan – Apples (Article 21.5 – US)*, para. 8.156 (concluding that because the 2004 PRA did not amount to a risk assessment as appropriate to the circumstances, Japan's measure was not based on a risk assessment).

[661] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

information" on the basis of which the provisional prohibition regarding these five hormones has been enacted. Consequently, the European Communities claims that, through Directive 2003/74/EC, it has implemented the rulings and recommendations in the *EC – Hormones* case.[662]

7.552 **Canada** argues that the European Communities in this case has failed to present any evidence to the Panel demonstrating that it meets any of the four requirements recalled by the Appellate Body in order to comply with Article 5.7 of the *SPS Agreement*.

7.553 For Canada, in the case of the five hormones at issue, the body of scientific evidence relating to these substances is such that the European Communities cannot plausibly argue that there is "insufficient" scientific evidence to conduct an adequate assessment of risk. The five hormones banned by the European Communities have been the subject of several scientific assessments by reputable national regulatory agencies and international expert scientific committees, such as JECFA. Therefore, the EC contention that there is insufficient scientific evidence to conduct a risk assessment is unfounded, given that reputable international bodies of scientific experts have in fact already performed risk assessments on the basis of the scientific information at their disposal.

7.554 Canada recalls that the second requirement for justifying a measure as a provisional measure under Article 5.7 is that the measure must be adopted "on the basis of available pertinent information, including that from the relevant international organizations as well as from sanitary or phytosanitary measures applied by other Members". In the present case, an objective analysis of the "available pertinent information" regarding the health risks associated with residues of these hormones in meat derived from animals treated with growth hormones, including information from relevant international organizations and SPS measures applied by other Members, does not reasonably support the European Communities' ban on these five hormones.

7.555 Canada notes that the first sentence of Article 5.7 also requires that Members consider available pertinent information from "relevant international organizations" as a basis for adopting a provisional SPS measure. Based on the scientific assessments conducted by JECFA in respect of these five substances as well as the adoption of Codex standards regarding these hormones, the EC measure, which continues the ban on these hormones for growth-promotion purposes, is not based on the available pertinent information.

7.556 Canada argues further that, under the second sentence of Article 5.7, the European Communities has an explicit obligation to collect additional information in order to review more objectively the appropriateness of its ban on these hormones. In this case, the European Communities has not demonstrated that it is complying with its obligations under the second sentence of Article 5.7 of the *SPS Agreement*. Although the Directive specifically indicates that the Commission shall seek additional information from all possible sources, the EC has provided no evidence of its efforts to obtain the necessary information to conduct a proper risk assessment.[663]

7.557 The **European Communities** argues that, since the *EC – Hormones* case, the body of evidence has developed and, while still not providing enough knowledge to carry out a complete and definitive risk assessment, supports the conclusion that precautionary measures are required in order to achieve its chosen level of protection.

7.558 According to the European Communities, the evidence, while pointing to a number of risks, is full of gaps in pertinent information and important contradictions have developed that render no longer valid the conclusions reached by JECFA in 1988, 1999 and 2000, thus not allowing a quantitative or qualitative risk assessment. According to the European Communities, a number of

[662] EC's first written submission, para. 17.
[663] Canada's first written submission, paras. 109-131.

significant scientific developments, taken together with all other available evidence, indicates that it is not possible to undertake a definitive risk assessment for the five hormones concerned.

7.559 **Canada** replies that the European Communities provides no explanation of the alleged *lacunae* in the relevant scientific evidence leading to its assertion, preferring instead to refer to the recitals of its measure which do not provide any added information in this regard.

7.560 Canada argues that it has demonstrated that there is a vast body of relevant scientific evidence on the safety of these five hormones when used for growth promotion purposes. The European Communities has not demonstrated why it considers that, for example, the JECFA studies have yielded unreliable scientific evidence. The European Communities seems to suggest that the simple passage of time is sufficient to invalidate previously held scientific opinions. But the European Communities does not provide any reasons why the Codex standards and the JECFA studies should be considered to be based on "insufficient", scientific evidence. While maintaining that there is a lack of evidence pertaining to these issues, the European Communities disregards basic facts related to the hormones themselves and the numerous scientific reviews that they have undergone.

7.561 According to Canada, the European Communities fails to adequately explain why it has adopted a measure banning the use of the five hormones for growth promotion purposes when JECFA and the Codex Alimentarius Commission have conducted safety assessments and adopted international standards that attest to the safety of these substances.

7.562 Canada adds that in situations where some evidence of risk exists but not enough to complete a full risk assessment, a Member is not free to adopt any measure it wishes; it must adopt a measure based on what scientific evidence exists concerning the SPS issue in question, including information from relevant international organizations. In the present case, the European Communities has failed to demonstrate that there is a rational relationship between its ban on the five hormones in question and the available pertinent information from JECFA and the Codex Alimentarius Commission.

7.563 Canada agrees with the European Communities that the length of the reasonable period of time to review the appropriateness of the provisional SPS measures may vary from case to case depending on the difficulty in obtaining additional information and the characteristics of the SPS measure at issue. However, a Member's domestic legislative procedures may not have any impact on the determination of the reasonable period of time. In cases of a total import ban such as the one facing Canada, the reasonable period of time to review the provisional measure should be determined so as to minimize the extent of the trade impact of such a measure which is not based on a full risk assessment and was, by implication, adopted without sufficient scientific evidence.

7.564 Canada notes that the European Communities is allegedly seeking the additional information necessary for a more objective assessment of risk. However, more than two years have passed since the adoption of the EC new directive banning the use of the five hormones in question. Yet the European Communities has provided no explanation as to how it has reviewed its measure in the light of the new information available since the adoption of the new EC Directive.[664]

(iii) Approach of the Panel

7.565 As a first remark, the Panel recalls its conclusion that the measure at issue, to the extent that it provisionally bans the import of meat from cattle treated with the hormones progesterone,

[664] Canada's second written submission, paras. 112-146.

testosterone, trenbolone acetate, melengestrol acetate and zeranol, is an SPS measure within the meaning of Article 1 of, and paragraph 1 of Annex A to, the *SPS Agreement*.[665]

7.566 Second, both parties address the issue of the compatibility of the provisional ban on the above-mentioned five hormones with the provisions of Article 5.7 of the *SPS Agreement*. None of the parties discussed the compatibility of the ban imposed with respect to these five hormones with Article 5.1.[666] The Panel will therefore limit its review to the conformity of the EC ban on the five hormones with the requirements of Article 5.7.

7.567 Article 5.7 of the *SPS Agreement* provides as follows:

> "In cases where relevant scientific evidence is insufficient, a Member may provisionally adopt sanitary ... measures on the basis of available pertinent information, including that from the relevant international organizations as well as from sanitary ... measures applied by other Members. In such circumstances, Members shall seek to obtain the additional information necessary for a more objective assessment of risks and review the sanitary ... measure accordingly within a reasonable period of time."

7.568 In *Japan – Agricultural Products II*, the Appellate Body recalled that Article.5.7 "set[s] out four requirements that must be satisfied in order to adopt and maintain a provisional measure." These requirements are:

(a) the measure is imposed in respect to a situation where "relevant scientific evidence is insufficient";

(b) the measure is adopted "on the basis of available pertinent information";

(c) the Member which adopted the measure must "seek to obtain the additional information necessary for a more objective assessment of risk"; and

(d) the Member which adopted the measure must "review the ... measure accordingly within a reasonable period of time".[667]

7.569 The Appellate Body noted that the four requirements are "clearly cumulative in nature", and that "[w]henever *one* of these four requirements is not met, the measure at issue is inconsistent with Article 5.7."[668]

7.570 The Panel recalls that previous panels have addressed each of these requirements successively. Having regard to our duty to review the situation for each of the five hormones concerned by the provisional ban, we will proceed first with the examination of the requirement under

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[665] See para. 7.425 above.

[666] The Panel asked a question to the parties on a possible "automatic" violation of Articles 2.2 and 5.1 as a result of a violation of Article.5.7 (second series of questions from the Panel to the parties, question 2). The Panel notes, however, that neither the European Communities nor Canada requested the Panel to review the compatibility of the EC implementing measure regarding the five hormones subject to a provisional ban with Article 5.1 or Article 2.2. The Panel also notes that the EC implementing measure is supposed to have removed the violation of Article 5.1 through the adoption of a provisional ban compatible with Article 5.7. In light of our approach to the aspect of this case relating to the compatibility of the EC implementing measure with the *SPS Agreement*, we decided to limit our review to the compatibility of this measure with Article 5.7.

[667] *See* Appellate Body Report on *Japan – Apples*, para. 176, citing the Appellate Body Report on *Japan – Agricultural Products II*, para. 89.

[668] Appellate Body Report on *Japan – Agricultural Products II*, para. 89.

(a) above, i.e. whether the measure is imposed with respect to a situation where "relevant scientific evidence is insufficient".

7.571 Moreover, having regard to the arguments of the parties and in line with our duty not to perform a *de novo* risk assessment, we will limit ourselves to review the issues with respect to which the parties exchanged arguments and provided sufficient evidence.

7.572 We also note that Canada's main line of argumentation is that the body of scientific evidence relating to the substances at issue is such that "the European Communities cannot plausibly argue that there is 'insufficient' scientific evidence to conduct an adequate assessment of risk. The five hormones banned by the European Communities have been the subject of several scientific assessments by reputable national regulatory agencies and international expert scientific committees, such as JECFA."[669] In that context, we deem it appropriate to determine to what extent relevant scientific evidence can become insufficient within the meaning of Article 5.7 in the presence of international standards.

7.573 The Panel does not believe that the issue of the possibility or not to make a *quantitative* estimate of the risk to consumers constitutes a subject on which a discussion of whether "relevant scientific evidence is insufficient" is needed. The Panel recalls in this respect that the standard applied by the Appellate Body to determine whether relevant scientific evidence is insufficient is that:

> " 'relevant scientific evidence' will be 'insufficient' within the meaning of Article 5.7 if the body of available scientific evidence does not allow, *in quantitative or qualitative terms*, the performance of an adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*."[670]

7.574 Moreover, we note that the Appellate Body considered that Article 5.1 does not require that risk assessments be quantitative, but that qualitative risk assessments are also compatible with Article 5.1.[671] We recall in this regard that Codex itself does not necessarily require the performance of quantitative risk assessments.[672]

7.575 We also deem it important to recall that, in *Japan – Agricultural Products II*, the Appellate Body stated that:

> "Article 5.7 allows members to adopt provisional SPS measures '[i]n case where relevant scientific evidence is insufficient' and certain other requirements are fulfilled. Article 5.7 operates as a qualified exemption from the obligation under Article 2.2 not to maintain SPS measures without sufficient scientific evidence. An overly broad and flexible interpretation of that obligation would render Article 5.7 meaningless."[673]

7.576 The European Communities also refers to paragraphs 194 (on minority scientific views) and 205 (on Article 5.2 and good veterinary practices) of the report of the Appellate Body in *EC – Hormones*.

7.577 We have already addressed above[674] the question of the treatment of minority views among experts and do not find it necessary to come back on this matter. As far as the second issue is

[669] Canada's first written submission, paras. 117-118.
[670] Appellate Body Report on *Japan – Apples*, para. 179 (emphasis added).
[671] Appellate Body Report on *EC – Hormones*, para. 187.
[672] Working Principles for Risk Analysis for Application within the Framework of the Codex Alimentarius, para. 20.
[673] Appellate Body Report on *Japan – Agricultural Products II* , para. 80.
[674] See para. 7.411 above.

concerned, we note that, as recalled by the Appellate Body in *EC – Hormones*, it is also appropriate for the European Communities to consider situations of misuse:

> "… The *SPS Agreement* requires assessment of the potential for adverse effects on human health arising from the presence of contaminants and toxins in food. We consider that the object and purpose of the *SPS Agreement* justify the examination and evaluation of all such risks for human health whatever their precise and immediate origin may be. We do not mean to suggest that risks arising from potential abuse in the administration of controlled substances and from control problems need to be, or should be, evaluated by risk assessors in each and every case. When and if risks of these types do in fact arise, risk assessors may examine and evaluate them. Clearly, the necessity or propriety of examination and evaluation of such risks would have to be addressed on a case-by-case basis. What, in our view, is a fundamental legal error is to exclude, on an *a priori* basis, any such risks from the scope of application of Articles 5.1 and 5.2 …"[675]

7.578 The above statement was made in relation to the performance of a risk assessment under Article 5.1 and 5.2 of the *SPS Agreement*. We recall that Article 5.7 is applicable when relevant scientific evidence is not sufficient to undertake a risk assessment in conformity with Article 5.1. Whether instances of misuse or abuse in the administration of hormones exist or not is not as such a scientific issue likely to make a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement* impossible. In our opinion, the scientific issue is related to the effect of the ingestion of high doses of hormones residues, not to potential or actual misuse or abuse in the administration of hormones. Therefore, we will not address the issue of non compliance with good veterinary practices in our analysis under Article 5.7 of the *SPS Agreement*.

(iv) When will "relevant scientific evidence" be deemed "insufficient"?

Effect of the level of protection on the consideration of the insufficiency of relevant scientific evidence under Article 5.7

7.579 According to the **European Communities**, whether a risk assessment can reach a definitive conclusion depends not only on the data available but also on how a risk assessment has been framed by the risk manager.[676] The European Communities argues that a Member may disagree with the risk assessment underlying an international standard for scientific reasons and, in particular, on the issue of whether the scientific evidence relied upon is sufficient. Such a disagreement may result from the fact that in order to meet a higher level of protection, a Member may require more information than that provided.[677] The European Communities argues that the evidence which served as the basis for the 1988 and 1999-2000 JECFA evaluations is not sufficient "to perform a definitive risk assessment within the meaning of Article 5.7, in particular by the WTO Members applying a high level of health protection of no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion".[678]

7.580 **Canada** is of the view that there is simply no basis for the EC approach in the text of the *SPS Agreement* or the relevant WTO jurisprudence. According to Canada, the European

[675] Appellate Body Report on *EC – Hormones*, para. 206. See also Appellate Body Report on *Japan – Apples*, para. 179.

[676] EC's oral statement at the second panel meeting, para. 22.

[677] EC's replies to Panel questions after the first substantive meeting, question 72, Annex B-1, para. 266.

[678] EC's second written submission, para.143; EC's replies to Panel questions after the first substantive meeting, question.31, Annex B-1, paras. 167-172.

Communities does not contest that these five hormones have been the subject of several scientific assessments by reputable regulatory agencies and international scientific committees such as JECFA. However, the European Communities seems to be at a loss to explain why in the face of these risk assessments it has concluded that it is unable to perform an adequate assessment of risk on these five hormones. The European Communities discounts the valid scientific findings of JECFA in respect of the safety of these hormones on the basis that the JECFA findings do not meet the European Communities' chosen level of protection. In doing so, the European Communities confuses the notion of the "insufficiency", or in the present case the "sufficiency", of the relevant scientific evidence with a WTO Member's "autonomous right"[679] to establish its own appropriate level of protection as set out in Article 3.3 of the *SPS Agreement*.

7.581 In Canada's opinion the ability to conduct a risk assessment cannot hinge on a Member's appropriate level of protection. Such an approach undermines the basic logic of the *SPS Agreement* as reflected in Articles 2.2, 3.3, 5.1 and 5.7 of the Agreement. Article 3.3 requires that where a Member introduces a measure that results in a higher level of SPS protection than that implied by the relevant international standards, it must base its measure on a risk assessment.

7.582 Canada considers that a Member cannot refuse to consider certain relevant scientific evidence in its evaluation of whether or not the body of available scientific evidence is sufficient to allow the performance of a risk assessment on the basis that this evidence does not achieve the Member's chosen level of protection. Such an approach would allow Members to arbitrarily set their level of protection so high that they could effectively exclude from the pool of relevant scientific evidence any evidence that does not meet their chosen level of protection. This does not conform with the test set out by the Appellate Body with regard to the sufficiency of the "relevant scientific evidence" under Article 5.7.[680]

7.583 The **Panel** first notes that the European Communities refers to the fact that the evidence is not sufficient to perform a "definitive risk assessment". However, the European Communities nowhere defines what it means by a "definitive risk assessment". The Panel recalls the definition of adequate risk assessment proposed by the European Communities in *EC – Approval and Marketing of Biotech Products*: "one which has been 'delivered by a reputable source, [which] unequivocally informs the legislator about what the risk is with a sufficient degree of precision, and [which] has withstood the passage of time and is unlikely to be revised'."[681] It is unclear to the Panel whether this is what the European Communities refers to in this case as a "definitive risk assessment". The Panel would like to specify that there is no obligation under the *SPS Agreement* to perform a *definitive* risk assessment for that risk assessment to be valid under Article 5.1. Moreover, the Panel doubts that a *definitive* risk assessment can in practice ever be performed, since new evidence becomes available and risk assessments may need to be reviewed and updated accordingly, or else the measure based on these risk assessments will have to be adjusted to the evolution of the scientific evidence.[682] The Panel understands the terms "based on an assessment, as appropriate to the circumstances" to suggest that the link between the SPS measure adopted by a Member and the risk assessment on which it is based may evolve depending on the circumstances, thus implying that Article 5.1 does not require a definitive risk assessment. This is also confirmed by the fact that risk assessments do not have to be "monolithic" as recalled by the Appellate Body in *EC – Hormones*.[683] In any event, the criterion allowing the adoption of sanitary measures on the basis of available pertinent information under Article 5.7 is that "relevant scientific evidence is insufficient" to permit the performance of a risk assessment as required under Article 5.1 and Annex A(4), not that the risk assessment to be performed

[679] Appellate Body Report on *EC – Hormones*, para. 172.
[680] Canada second written submission, para. 128.
[681] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.3238.
[682] See Panel Report on *EC – Approval and Marketing of Biotech Products*, paras. 7.3239-7.3240.
[683] Appellate Body Report on *EC – Hormones*, para. 194.

pursuant to Article 5.1 be a definitive one.[684] The Panel is of the view that, by suggesting that a risk assessment be definitive, the European Communities actually disregards the Appellate Body interpretation mentioned above and seeks to impose a higher threshold for compliance with Article 5.1, or a lower one to meet the conditions of Article 5.7. However, the Panel does not believe that this approach is supported by Article 5.1, Annex A(4) or Article 5.7.

7.584 The Panel also notes the EC view that, in determining whether the relevant scientific evidence is insufficient, within the meaning of Article 5.7, the Panel should take into account the level of health protection applied by the Member concerned. More particularly, the European Communities argue that, when the level of health protection of a Member is particularly high and the body of evidence is in the process of moving from a state of sufficiency to a state of insufficiency, that Member should not be required to demonstrate positively the existence of a clear harm.

7.585 Regarding the issue of whether the level of health protection of a particular Member should play a role in its assessment of whether the relevant scientific evidence is insufficient, the Panel notes that the EC level of health protection is that of "no (avoidable) risk, that is a level of protection that does not allow any unnecessary addition from exposure to genotoxic chemical substances that are intended to be added deliberately to food."[685]

7.586 We recall that the Appellate Body in *Japan – Apples* stated that relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*.[686]

7.587 The terms of Article 5.1 and Annex A to the *SPS Agreement* and, in particular, the definition of "risk assessment" do not indicate that a Member's level of protection is pertinent to determine whether a risk assessment can be performed or not. We agree with the Panel in *EC – Approval and Marketing of Biotech Products* when it states that:

> "[W]e are not convinced that the protection goals pursued by a legislator are relevant to such a determination. The protection goals of a legislator may have a bearing on the question of which risks a Member decides to assess with a view to taking regulatory action, if necessary. And a legislator protection goals are certainly relevant to the determination of the measure ... to be taken for achieving a Member's level of protection against risk. Yet there is no apparent link between a legislator's protection goals and the task of assessing the existence and magnitude of potential risks."[687]

7.588 We note that sufficient scientific evidence is what is needed to make a risk assessment. The assessment whether there is sufficient scientific evidence or not to perform a risk assessment should be an objective process. The level of protection defined by each Member may be relevant to

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[684] The Panel notes in this respect that in *Australia – Salmon*, the Appellate Body stated that:

> "We might add that the existence of unknown and uncertain elements does not justify a departure from the requirements of Articles 5.1, 5.2 and 5.3, read together with paragraph 4 of Annex A, for a risk assessment."(Appellate Body Report on *Australia – Salmon*, para. 130).

The Panel also notes Dr. Boisseau's remark, that "it is always possible to ask for more data in order to clarify more issues so that the will to eliminate any scientific uncertainty could result in an endless assessment process". Replies by the scientific experts to Panel questions, para. 452, Annex D.

[685] EC's replies to Panel questions after the second substantive meeting, Annex C-1, para. 69.

[686] Appellate Body Report on *Japan – Apples*, para. 179.

[687] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.3238.

determine the measure to be selected to address the assessed risk, but it should not influence the performance of the risk assessment as such.

7.589 Indeed, whether a Member considers that its population should be exposed or not to a particular risk, or at what level, is not relevant to determining whether a risk exists and what its magnitude is. *A fortiori*, it should have no effect on whether there is sufficient evidence of the existence and magnitude of this risk.

7.590 A risk-averse Member may be inclined to take a protective position when considering the measure to be adopted. However, the determination of whether scientific evidence is sufficient to assess the existence and magnitude of a risk must be disconnected from the intended level of protection.

7.591 This is not to say, however, that we disagree with the European Communities that when the body of evidence is in the process of moving from a state of sufficiency to a state of insufficiency a Member should not be required "to demonstrate positively the existence of clear harm."[688] In fact, even when the scientific evidence is sufficient, a Member is not required, under the provisions of the *SPS Agreement*, to "demonstrate positively the existence of a clear harm". Rather, the objective of a risk assessment is to evaluate the potential for harm to occur under certain circumstances (e.g., from the consumption of a foodstuff containing certain contaminants).

Can relevant scientific evidence *become* "insufficient"?

7.592 In reply to a question from the Panel, **Canada** argues that Article 5.7 applies when "no risk assessment can be made at all" either because there is simply not enough evidence to conduct a risk assessment, or when the evidence available is insufficiently specific to conduct a risk assessment as defined in Annex A of the *SPS Agreement*.[689]

7.593 Canada adds that it is theoretically possible that scientific evidence judged to be sufficient to undertake a risk assessment at a particular point in time may be considered to be insufficient to conduct a risk assessment for the same purpose several years later. For example, this could be due to a change in the basic understanding of a biological event that is triggered by the chemical under assessment, new scientific data that identify new adverse effects or adverse effects at lower exposure levels. New sources of exposure could also trigger the need to reassess the adequacy of the risk assessment.

7.594 Canada considers that it would not be the number of scientific studies conducted in the intervening years that would determine whether a new risk assessment was necessary but rather the nature of the studies. For example, if new residue studies (i.e. an analysis of the chemical and significant metabolites in food) were carried out then this would require minimally an exposure reassessment and possibly a risk characterization reassessment. [690]

7.595 The **European Communities** considers that Article 5.7 of the *SPS Agreement* is applicable not only when no risk assessment can be made at all, but also when the latest scientific evidence from any credible and objective source raises doubts or puts into question the previously held scientific opinion about the safety or dangerous nature of the substance in question.[691] The European Communities adds that the evidence assessed by the SCVPH, while inconclusive in terms of demonstrating a risk, does nonetheless point to the possible occurrence of certain adverse effects,

[688] EC's second written submission, para. 149.
[689] Canada's replies to Panel questions after the first substantive meeting, question 67, Annex B-2.
[690] Canada's replies to Panel questions after the first substantive meeting, question 73, Annex B-2
[691] EC's replies to Panel questions after the first substantive meeting, question 67, Annex B-1.

which invalidate or put into serious doubts previously held assumptions about the safety of these hormones by the defending parties and Codex/JECFA.[692] The European Communities concludes that serious doubt may exist when the pertinent available evidence is contradictory, inconclusive or incomplete.[693] To guard against potential abuses, the new evidence should not be arbitrary but credible and should show that there is a genuine scientific disagreement identified in a risk assessment.

7.596 The European Communities further argues that, due to the dynamic nature of scientific knowledge, a risk assessment that may at one point in time have been based on sufficient scientific evidence may need to be reviewed when new scientific evidence becomes available. In addition, new international risk assessment standards may become available that have to be taken into account in new risk assessments.[694]

7.597 First, the **Panel** notes that parties agree to the fact that scientific evidence which was previously deemed sufficient could subsequently become insufficient. Both parties agree that there could be situations where new studies can affect the conclusion of existing risk assessments. Canada considers, however, that in the case at hand the existence of such new studies would not make the scientific evidence "insufficient" for conducting such an assessment.

7.598 The Panel agrees with the parties that there could be situations where existing scientific evidence can be put in question by new studies and information. There could even be situations where evidence which supported a risk assessment is unsettled by new studies which do not constitute sufficient relevant scientific evidence as such to support a risk assessment but are sufficient to make the existing, previously relevant scientific evidence insufficient.[695]

7.599 Indeed, nothing in Article 5.7 prevents such an interpretation. We also note in this respect that Article 2.2 foresees such a possibility when it mentions that sanitary measures must not be "*maintained* without sufficient scientific evidence except as provided for in paragraph 7 of Article 5."[696] The use of the word "maintained" read together with the reference to Article 5.7 suggests the possibility of an evolution from a situation of sufficient evidence to perform a risk assessment to one where, in substance, a risk assessment can no longer be performed.

7.600 The Panel notes in this respect that a procedure is available for Codex members and observers to request the inclusion of a particular compound for evaluation or re-evaluation on a "priority list" that the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) communicates to JECFA.[697] The European Communities refers to an exchange of letters between the European Commission and Codex and JECFA regarding a postponement of the re-evaluation due to be carried out by JECFA in 1999.[698] The European Communities seems to allege that there was a commitment from Codex and JECFA to re-evaluate the hormones at issue once the studies commissioned by the European Communities would be available.[699] However, this explanation was not confirmed by

[692] EC's second written submission, para. 143.
[693] EC's replies to Panel questions after the second substantive meeting, Annex C-1, para. 43.
[694] EC's replies to Panel questions after the first substantive meeting, question 73, Annex B-1, paras. 268-273.
[695] See also Article 2.2 which provides that a sanitary measure must not be maintained without sufficient scientific evidence except as provided for in paragraph 7 of Article 5. This seems to imply that the information relied upon under Article 5.7 may include evidence, including relevant scientific evidence and not merely information, as long as that evidence remains insufficient.
[696] Emphasis added.
[697] See statement of Dr. Miyagishima, Codex representative, Transcript of the Panel meeting with the experts, Annex G, paras. 523-524.
[698] Exhibit EC-63.
[699] EC's statement, Transcript of the Panel meeting with the experts, Annex G, para. 527.

Codex or JECFA. From the information communicated by the representatives of Codex and JECFA at the meeting of the Panel with scientific experts, it appears on the contrary that the European Communities never actually requested Codex or JECFA to re-evaluate any of the hormones for which risk assessments had been carried out by JECFA and standards adopted by Codex. The representative of Codex stated that there was no record in the reports of the CCRVDF of proposals, either from the European Communities or from Member States of the European Communities, to include the five substances at issue in the priority list for re-evaluation by JECFA.[700] The representative of Codex added that, even at the latest session of the CCRVDF in 2006, no such request had been made.[701]

7.601 Second, since the present situation is one where it is alleged that existing relevant scientific evidence has become insufficient, it seems important to determine which circumstances could make such existing evidence insufficient.

7.602 The Panel recalls that, in *Japan – Apples*, the Appellate Body found that:

> " '[R]elevant scientific evidence' will be "insufficient" within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*. Thus, the question is not whether there is sufficient evidence of a general nature or whether there is sufficient evidence related to a specific aspect of a phytosanitary problem, or a specific risk. The question is whether the relevant evidence, be it 'general' or 'specific', in the Panel's parlance, is sufficient to permit the evaluation of the likelihood of entry, establishment or spread of, in this case, fire blight in Japan."[702]

7.603 We also note that in *EC – Approval and Marketing of Biotech Products*, the panel stated that:

> "[I]t must be determined on a case-by-case basis whether the body of available scientific evidence is insufficient to permit the performance of a risk assessment."

7.604 We agree with the *EC – Approval and Marketing of Biotech Products* panel and we will base our assessment on the evidence submitted by the parties in this case, having regard to the views of the experts on each issue.

7.605 This said, the Panel believes that it needs to determine under which circumstances relevant scientific evidence may more particularly be deemed "insufficient" in this case.

7.606 The Panel first reads the first sentence from the extract of the Appellate Body report in *Japan – Apples* quoted above as meaning that relevant scientific evidence will be deemed insufficient within the meaning of Article 5.7 if the relevant scientific evidence does not make it possible to complete a risk assessment on which a sanitary measure can be based *in substance*. It is always possible to perform the four successive steps of a risk assessment as defined by Codex and ultimately reach the conclusion that relevant scientific evidence is insufficient (as the European Communities did in the case of the five hormones in respect of which it applies a provisional ban). However, the fact that the Codex four steps can be formally completed does not mean that such a process is equated with a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*. There will be a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement* when the

[700] Statement by Dr. Miyagishima, Codex representative, Transcript of the Panel meeting with the experts, Annex G, para. 524.
[701] Dr. Miyagishima, Codex representative, Transcript of the Panel meeting with the experts, Annex G, para. 529.
[702] Appellate Body Report on *Japan – Apples*, para. 179.

assessor has analysed fully the potential for the identified adverse effects to arise from the presence of the substance at issue in food, beverages, or foodstuffs. We believe that this was the intention of the Appellate Body when it used the term *adequate*[703] in "adequate assessment of risks as required under Article 5.1 and as defined in Annex A to the *SPS Agreement*." This is confirmed by the second sentence of Article 5.7 which provides that "Members shall seek to obtain the additional information necessary for a *more objective assessment* of risk."[704] In other words, Article 5.7 will apply in situations where, in substance, the relevant scientific evidence does not allow the completion of an objective evaluation of the potential for adverse effects on human or animal health arising from the presence of additives, contaminants, toxins or disease-causing organisms in food, beverages or feedstuffs.

7.607 While this gives a general idea of the circumstances under which Article 5.7 may be invoked, we should strive to ascertain more precisely the scope of "insufficient", if possible. In doing that, we should keep in mind that Article 5.7 operates as a qualified exemption from the obligation under Article 2.2 not to maintain SPS measures without sufficient scientific evidence and that an overly broad and flexible interpretation of that obligation would render Article 5.7 meaningless.[705]

7.608 As a first step, we note that, in *Japan – Apples*, the Appellate Body seemed to consider that *relevant* scientific evidence is insufficient if, irrespective of the quantity of evidence available, it has not led to *reliable* or *conclusive* results.[706] It also seems that evidence providing unreliable or inconclusive results should not be confused with "scientific uncertainty", as it appears from the following Appellate Body statement in *Japan – Apples*:

> "The application of Article 5.7 is triggered not by the existence of scientific uncertainty, but rather by the insufficiency of scientific evidence. The text of Article 5.7 is clear: it refers to 'cases where relevant scientific evidence is insufficient', not to 'scientific uncertainty'. The two concepts are not interchangeable."[707]

7.609 We understand this statement to mean that the existence of scientific uncertainty does not automatically amount to a situation of insufficiency of relevant scientific evidence. In other words, the fact that a number of aspects of a given scientific issue remain uncertain may not prevent the performance of a risk assessment. First, we should exclude theoretical uncertainty, which is the uncertainty that always remains because science can never provide absolute certainty about the safety of a given substance. In *EC – Hormones*, the panel and the Appellate Body concurred in agreeing that theoretical uncertainty was not the kind of risk to be assessed under Article 5.1.[708] In the Panel's view, theoretical uncertainty therefore should also not determine the applicability of Article 5.7.

7.610 Second, we note that in *EC – Hormones*, the Appellate Body stated that the presence of divergent views on an issue could be a form of scientific uncertainty.[709] We nevertheless note that

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[703] "commensurate in fitness, sufficient, satisfactory" (*The Shorter Oxford English Dictionary* (5th ed., 2002), p. 26).
[704] Emphasis added.
[705] Appellate Body Report on *Japan – Agricultural Products II*, para. 80.
[706] Appellate Body Report on *Japan – Apples*, para. 185:

> "We do not read the Panel's interpretation as excluding cases where the available evidence is more than minimal in quantity, but has not led to reliable or conclusive results."

[707] Appellate Body Report on *Japan – Apples*, para. 184.
[708] Appellate Body Report on *EC – Hormones*, para. 186.
[709] Appellate Body Report on *EC – Hormones*, para. 194.

scientific uncertainty may be factored into the conclusions of the risk assessment. We find support for this conclusion in the following comment of the Appellate Body in *Australia – Salmon*:

> "We might add that the existence of unknown and uncertain elements does not justify a departure from the requirements of Articles 5.1, 5.2 and 5.3, read together with paragraph 4 of Annex A, for a risk assessment."[710]

7.611 This issue was further addressed by the panel in *EC – Approval and Marketing of Biotech Products*, which acknowledged that the conclusions of a risk assessment may not be free from uncertainties or other constraints even though there was sufficient relevant scientific evidence to perform the risk assessment.[711] The panel, in agreement with the Appellate Body in *EC – Hormones*, found "that such uncertainties may be legitimately taken into account by a Member when determining the SPS measure, if any, to be taken" and that the scientific uncertainties present in a risk assessment may support a range of possible measures and within the range of measures reasonably supported by the risk assessment and consistent with other applicable *SPS Agreement* provisions, the Member was entitled to choose one that best protects human health and/or the environment.[712] As recalled by the panel in *EC – Approval and Marketing of Biotech Products*, Members were also justified in taking into account factors like a limited body of relevant scientific evidence, assumptions and other constraints that would affect the level of confidence in the risk assessment:

> "We consider that if there are factors which affect scientists' level of confidence in a risk assessment they have carried out[713], a Member may in principle take this into account in determining the measure to be applied for achieving its appropriate level of protection from risks.[714] Thus, there may conceivably be cases where a Member which follows a precautionary approach, and which confronts a risk assessment that identifies uncertainties[715] or constraints, would be justified in applying (i) an SPS measure even though another Member might not decide to apply any SPS measure on

[710] Appellate Body Report on *Australia – Salmon*, para. 130.
[711] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.1525.
[712] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.1525.
[713] (*footnote original*) *E.g.*, a limited body of relevant scientific evidence may be such a factor.
[714] (*footnote original*) This view is consistent with risk assessment techniques established by relevant international organizations. For instance, the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* state that "[t]he report of the risk assessment should indicate any constraints, uncertainties, assumptions and their impact on the risk assessment. Minority opinions should also be recorded. The responsibility for resolving the impact of uncertainty on the risk management decision lies with the risk manager, not the risk assessors". Codex Alimentarius Commission, *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* (adopted in June/July 2003), Section III, Codex Procedural Manual, 14th edition, 2004, para. 25. Along similar lines, the Codex *Principles for the Risk Analysis of Foods Derived from Modern Biotechnology* state that "[r]isk managers should take into account the uncertainties identified in the risk assessment and implement appropriate measures to manage these uncertainties". Codex Alimentarius Commission, *Principles for the Risk Analysis of Foods Derived from Modern Biotechnology* (adopted in June/July 2003), CAC/GL 44-2003, para. 18. Similarly, the IPPC's ISPM #11 (2001) states in relevant part that "[t]he uncertainty noted in the assessments of economic consequences and probability of introduction should also be considered and included in the selection of a pest management option". IPPC, ISPM #11: *Pest Risk Analysis for Quarantine Pests*, April 2001, para. 3. The quoted passage stayed the same in the 2004 version of ISPM #11, which applies specifically to living modified organisms.
[715] (*footnote original*) We are not referring here to the theoretical uncertainty which inevitably remains because science can never provide absolute certainty that a product will never have adverse effects on human health or the environment. The Appellate Body has made it clear that this theoretical uncertainty is not the kind of risk which is to be assessed under Article 5.1. Appellate Body Report on *EC – Hormones*, para. 186.

> the basis of the same risk assessment, or (ii) an SPS measure which is stricter than the SPS measure applied by another Member to address the same risk".[716]

7.612 The panel explicitly recognized that, even though scientific uncertainty existed, there could still be sufficient scientific evidence to perform a risk assessment.[717]

7.613 We note in this respect the comments of Dr. Boisseau and Dr. Boobis before the Panel on how scientific uncertainty is addressed in risk assessment.[718]

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[716] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.3065.
[717] Panel Report on *EC – Approval and Marketing of Biotech Products*, para. 7.1525.
[718] See replies of Dr. Boisseau and Dr, Boobis to question 12 of the Panel, Annex D, paras. 123-128.

Dr. Boisseau expressed the following views:

> "In assessing the risk for human health associated with the exposure to veterinary drug residues, JECFA adresses the scientific uncertainty by using the safety factors listed above in my reply to the question n°8 describing, among others, how JECFA builds a margin of safety into its final recommendations.
> For the hormonal growth promoters, JECFA has considered that, given the quality and the quantity of the available data, it was possible to carry out a complete quantitative risk assessment. For establishing ADIs and MRLs for the three synthetic hormones, melengestrol, trenbolone and zeranol, JECFA has implemented the usual procedure regarding the safety factors. For the three natural hormones, oestradiol-17β, progesterone and testosterone, JECFA has decided that the margin of safety deriving from the values of the established ADIs and from a maximum estimated intake of residue was such that it was not necessary to set up MRLs.
> For oestradiol-17β, the European Communities did not consider any scientific uncertainty as it decided that it was not possible, for reason of principle, to establish an ADI for a genotoxic compound. For the five other hormones at issue, the European Communities did not really consider any scientific uncertainty as it decided that the available data were too limited to allow a complete quantitative risk assessment to be carried out."

Dr. Boobis mentioned the following:

> "Scientific uncertainty is dealt with in a variety of ways in risk assessment. ...
>
> One way of dealing with uncertainty is to default to the worst case in the absence of evidence to the contrary. Hence, the most sensitive relevant endpoint in the most sensitive species is used as the basis of the risk assessment. In extrapolating to humans a default factor of 10 is used to allow for species differences, which assumes that humans are more sensitive than the experimental species. A further factor of 10 is included for interindividual differences. These differences may be due to gender, genetics, life stage or other factors. However, to some extent such differences have already been taken into account in the choice of endpoint, as this will usually represent the most sensitive lifestage, gender and to some extent genetics by using data from the most sensitive species. Where there are additional uncertainties, such as no NOEAL or the absence of a non-critical study, an additional safety factor will be included, and this is almost always conservative, as when the data gaps have been completed, the appropriate safety factor is almost always less than that used to account for these data gaps. The residue may be assumed to be all as active as the most active moiety, which is almost always a conservative assumption. Dietary intake is based on conservative data for food consumption. It is also assumed that all meat that could contain veterinary drug residue will contain the residue and that this will be present at the high end of the range (MRL or other appropriate level). In respect of the ADI, the assumption is that intake will be at this high level for a lifetime, when in reality there will be occasions when little or no meat is consumed

7.614 We find further support for this position in the view of the Appellate Body as expressed in *Japan – Apples* that whether relevant scientific evidence is insufficient must be assessed "not in the abstract, but in the light of a particular inquiry".[719]

7.615 While we agree that under certain circumstances what was previously sufficient evidence could become insufficient, we do not believe that the existence of scientific uncertainty means that previously sufficient evidence has in fact become insufficient, nor should it *ipso facto* justify the applicability of Article 5.7 of the *SPS Agreement*.

Relationship between insufficiency of the evidence and the existence of an international standard

7.616 **Canada** considers that it is essential to take international standards into consideration when determining whether relevant scientific evidence is insufficient. More important than the numerical standard is the basis, support or risk assessment for that international standard. For example, it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues.[720]

7.617 According to Canada, Article 5.7 allows Members to adopt provisional measures in a situation where there is insufficient scientific evidence to conduct a risk assessment. However, it does not give Members *carte blanche* in this area. The provisional measure must be based on "available pertinent information", including that from relevant international organizations and measures of other WTO Members. Where a relevant international organization has adopted standards on a particular SPS issue, it makes it extremely difficult for a Member to argue that there is insufficient scientific evidence to conduct a risk assessment, because the existence of an international standard implies that sufficient scientific evidence exists to complete a risk assessment. The burden rests with the European Communities in this case to demonstrate that, despite the adoption of international standards by Codex regarding the hormones at issue, the scientific evidence is insufficient to allow it to conduct a risk assessment.[721]

> or that which is consumed contains less or even no residue. In their risk assessment of the hormones, JECFA applied all of these approaches to dealing with the uncertainty.
>
> In dealing with scientific uncertainty much depends on the expert judgment of the risk assessor. Issues such as biological coherence, whether effects are considered compound related, relevance to humans, the reliability of model systems at predicting effects in vivo all impact on the interpretation of the data. Within the EU, it is clear that there are also differences in the interpretation of data, as illustrated by the differing conclusions of the CVMP (1999) and the SCVPH (1999). In part, the EC assessment of the hormones did not go as far as including some of the considerations for uncertainty used by JECFA because of the conclusion that there was insufficient information to determine whether there was a threshold for the carcinogenic effects. However, for some of the compounds this was based on the results of a small number of non-standard tests of genotoxicity, with equivocal of very weak responses. It is not clear whether the EC applied a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking account the totality of the available data, as was the case by JECFA."

[719] Appellate Body Report on *Japan – Apples*, para. 179. See also Panel Report on *EC – Approval and Marketing of Biotech Products*, where the Panel "agree[ed] that it must be determined on a case-by-case basis whether the body of available scientific evidence is insufficient to permit the performance of a risk assessment." (para. 7.3238).

[720] Canada's replies to Panel questions after the first substantive meeting, question 73, Annex B-2.

[721] Canada's replies to Panel questions after the first substantive meeting, question 72, Annex B-2.

7.618 The **European Communities** argues that a Member may disagree with the risk assessment underlying an international standard for scientific reasons and, in particular, on the issue of whether the scientific evidence relied upon is sufficient. Such a disagreement may result from the fact that in order to meet a higher level of protection, a Member may require more information than that provided for the development of the international standard.[722]

7.619 The European Communities further argues that the relevant Codex standards on four of the five provisionally banned hormones are not capable of achieving the chosen high level of protection of the European Communities. According to the European Communities, the overall evidence and recent scientific developments have now "tipped the balance against the previously held assumption (by the defending parties and Codex/JECFA) that residues of these hormones in meat from animals treated for growth promotion pose no risk to human health". The European Communities argues that the evidence which served as the basis for the 1999-2000 JECFA evaluations is not sufficient "to perform a definitive risk assessment within the meaning of Article 5.7, in particular by the WTO Members applying a high level of health protection of no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion".[723]

7.620 Referring to the way in which JECFA addresses scientific uncertainty through safety factors, the European Communities states that there is "almost universal agreement that this approach is not scientifically correct". According to the European Communities, a state of uncertainty may result from a number of factors including lacking, incomplete or contradictory data; the quality of the data is more important than the quantity. An issue thought to be clear can become uncertain as more data become available. The European Communities argues that if uncertainty is understood in this sense, it cannot be addressed through safety factors, especially for countries applying a high level of health protection.[724]

7.621 Having regard to the arguments of the parties, the **Panel** deems it important to recall that international standards, guidelines or recommendations exist with respect to four out of the five hormones at issue in this section.[725] The Panel notes in this respect the important role given to international standards, guidelines or recommendations by the *SPS Agreement*.[726] We also note that Article 3.2 of the *SPS Agreement* reads as follows:

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[722] EC's replies to Panel questions after the first substantive meeting, Annex B-1, para. 266.

[723] EC's second written submission, paras. 143; EC's replies to Panel questions after the first substantive meeting, question 31, Annex B-1, paras. 167-172.

[724] EC's comments on expert replies to Panel questions, question 12, Annex F-1.

[725] For melengestrol acetate, the situation is as follows: JECFA concluded its evaluation of MGA at its sixty-sixth meeting in Rome on 22-28 February 2006 and proposed MRLs. These MRLs were considered by CCRVDF in 2006, but because there was no consensus for their adoption, the CCRVDF agreed to consider them again at its session in 2007. (For more detail, including references to relevant Codex and JECFA reports, see Annex E-1, p. 103 and Annex E-2, p. 116). Annex A, paragraph 3 of the *SPS Agreement* defines international standards, guidelines and recommendations for food safety as follows:

"*International standards, guidelines and recommendations*

(a) for food safety, the standards, guidelines and recommendations established by the Codex Alimentarius Commission relating to food additives, veterinary drug and pesticide residues, contaminants, methods of analysis and sampling, and codes and guidelines of hygienic practice".

[726] See Article 3.1 of the *SPS Agreement*, which reads as follows:

"To harmonize sanitary and phytosanitary measures on as wide a basis as possible, Members shall base their sanitary or phytosanitary measures on international standards, guidelines or recommendations, where they exist, except as otherwise provided for in this Agreement, and in particular in paragraph 3." (Emphasis added)

> "Sanitary or phytosanitary measures which conform to international standards, guidelines or recommendations shall be deemed to be necessary to protect human, animal or plant life or health, and presumed to be consistent with the relevant provisions of this Agreement and of GATT 1994."

7.622 The presumption of consistency of measures conforming to international standards, guidelines and recommendations with the relevant provisions of the *SPS Agreement* implies that these standards, guidelines or recommendations, particularly those referred to in this case, are based on risk assessments that meet the requirements of the *SPS Agreement*. This means, therefore, that there was sufficient evidence for JECFA to undertake the appropriate risk assessments.

7.623 As mentioned above, the Panel is also mindful that science continuously evolves. It cannot be excluded that new scientific evidence or information call into question existing evidence. Likewise, it cannot be excluded that different risk assessments reach different interpretations of the same scientific evidence.

7.624 Yet, some meaning has to be given to the role assigned by the *SPS Agreement* to international standards, guidelines and recommendations, even though the rights of Members under Article 3.3 should be acknowledged[727], and this should not lead to the imposition of a special or generalized burden of proof upon the European Communities.[728]

7.625 As a result, we consider that, in order to properly take into account the existence of international standards, guidelines and recommendations in this case, our approach should be to assess whether scientific evidence has become insufficient by determining whether the European Communities has produced any evidence of some sufficient change in the scientific knowledge so that what was once sufficient to perform an adequate risk assessment has now become insufficient (i.e. "deficient in force, quality or amount")[729]. In this respect, suggesting hypothetical correlations or merely arguing that there could be more evidence on one concern or another should not be deemed sufficient to successfully claim that relevant scientific evidence has become *insufficient*. Indeed, more studies can always be performed and there can always be more evidence. We note in this regard that the European Communities shares our position in its second written submission, where it makes a "brief description of insufficiency of pertinent scientific information for all five hormones (except oestradiol-17β)". We interpret the use of the word "pertinent" and not "relevant" as in Article 5.7 as meaning that the European Communities agrees that not any insufficiency of relevant scientific evidence would make the performance of a risk assessment impossible. Indeed, "insufficiencies in the evidence" does not necessarily equal "insufficient evidence" to do a risk assessment, as recalled above. Moreover, as mentioned by the Appellate Body in *EC – Hormones*, risk assessments do not need to be based on "monolithic" evidence.

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[727] See Appellate Body Report on *EC – Hormones*, para.172. Article 3.3 of the *SPS Agreement* reads as follows:

> Members may introduce or maintain sanitary or phytosanitary measures which result in a higher level of sanitary or phytosanitary protection than would be achieved by measures based on the relevant international standards, guidelines or recommendations, if there is a scientific justification, or as a consequence of the level of sanitary or phytosanitary protection a Member determines to be appropriate in accordance with the relevant provisions of paragraphs 1 through 8 of Article 5. Notwithstanding the above, all measures which result in a level of sanitary or phytosanitary protection different from that which would be achieved by measures based on international standards, guidelines or recommendations shall not be inconsistent with any other provision of this Agreement. (original footnote omitted)

[728] Appellate Body Report on *EC – Hormones*, para.102. Regarding the allocation of burden of proof in relation to the *SPS Agreement* in this case, see paras. 7.377-7.383 above.

[729] *The New Shorter Oxford English Dictionary* (1993), p. 1384.

Conclusion

7.626 We therefore conclude that if relevant evidence already exists, not any degree of insufficiency will satisfy the criterion under Article 5.7 that "relevant scientific evidence is insufficient". Having regard to our reasoning above, particularly with respect to scientific uncertainty and the existence of international standards, we consider that, depending on the existing relevant evidence, there must be a *critical mass* of new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient, evidence now insufficient.[730] In the present case where risk assessments have been performed and a large body of quality evidence has been accumulated, this would be possible only if it put into question existing relevant evidence *to the point that* this evidence is no longer sufficient to support the conclusions of existing risks assessments. We therefore need to determine whether this is the case here.

(v) Alleged insufficiencies which should be addressed by the Panel

7.627 The **European Communities** argues that the most important gaps in the evidence are related to carcinogenicity, genotoxicity, dose-response and lack of safe thresholds, endogenous production by pre-pubertal children, lack of reliable bioavailability data, possibilities of abuse and lack of control. In addition, the European Communities maintains that since the latest SCVPH assessment, new scientific developments further support SCVPH conclusions.[731]

7.628 At this juncture, the **Panel** deems it appropriate to recall that parties have submitted a large amount of materials which was often very intricate and complex. The Panel believes that, as part of its obligations to make an objective assessment of the matter before it, including an objective assessment of the facts pursuant to Article 11 of the DSU, it had to devise an approach which would allow it to address the issues on which insufficiencies were alleged in a clear and transparent manner.

7.629 Whereas, in application of the burden of proof in relation to Article 5.7 of the *SPS Agreement*, it should be for the party challenging the applicability of Article 5.7 to make a prima facie case that the relevant scientific evidence regarding the five hormones is sufficient[732], it is also for the European Communities, in application of the principle that it is for each party to prove its allegations, to support its own allegations with appropriate evidence. This also has to be considered in the light of the fact that, even though in this case the European Communities is the complainant, it also argues as part of its allegations under Article 22.8 of the DSU that its implementing measure complies with Article 5.7 of the *SPS Agreement*. Moreover, we recall the consequence of the presumption of consistency with the *SPS Agreement* and GATT 1994 of measures which conform to international standards, guidelines and recommendations on the risk assessments on which such measures are based.[733] Since, in that context, the European Communities argues that the relevant scientific evidence is insufficient, we

[730] In its second written submission, at para. 149, the European Communities refers to the long latency period of cancer and the numerous confounding factors to claim that it may not be in a position to demonstrate the existence of a clear harm in case of cancer because of the long latency period and the numerous confounding factors that play a role in the development of cancer. We understand this argument to mean that we should accept the "new scientific reality" referred to by the European Communities as constituting a situation where relevant scientific evidence has become insufficient within the meaning of Article 5.7 of the *SPS Agreement*. We do not consider that our test amounts to requesting that the European Communities demonstrate the existence of a clear harm in order for Article 5.7 to apply to its measure. Under the "critical mass" test, the new scientific information and evidence must be such that they are at the origin of a change in the understanding of a scientific issue.

[731] EC's second written submission, paras. 137-138.

[732] *See* Appellate Body Report in *Japan – Agricultural Products II*, para.80; Panel Report in *Japan – Agricultural Products II*, para. 8.13*;* Panel Report in *EC – Approval and Marketing of Biotech Products*, paras. 7.2969-7.2979.

[733] See paras. 7.621-7.625.

consider that it is for the European Communities to identify the issues for which such evidence is insufficient.

7.630 Therefore, we do not consider that, as Panel, we have any obligation to go beyond the insufficiencies identified by the European Communities. We recall that we are neither equipped, nor supposed to make a *de novo* review of the scientific evidence regarding the hormones at issue. Under the circumstances, we deem it appropriate to limit our review exclusively to the "insufficiencies" expressly identified by the European Communities in its submissions to the Panel.

7.631 We note that, in its second written submission, the European Communities considers that the scientific evidence on which JECFA and Codex relied is insufficient with respect to the following issues: (a) carcinogenicity; (b) hormones daily production rate, in particular in pre-pubertal children; (c) dose response and lack of a safe threshold; (d) bioavailability; and (e) misuse or abuse (misplaced implants, off-label use, black market drugs, etc.).[734]

7.632 The European Communities also inserted in its replies to the first series of questions of the Panel and in its second written submission extensive portions of the 1999 and 2002 Opinions.[735]

7.633 In other words, the European Communities made its own description of the issues with respect to which it believes that evidence is insufficient and added quotations in support of its allegations. These passages also identify insufficiencies.

7.634 A number of issues discussed by the European Communities as part of the arguments contained in its submissions seem to overlap with the issues identified in the portions of the Opinions quoted by the European Communities. However, a number of specific issues identified in the quotations are simply not directly *discussed* by the European Communities in its submissions.

7.635 We believe that it is incumbent upon a party making a particular allegation to identify in its submissions the *relevance* of the evidence on which it relies to support its arguments.[736] We consider that, for some of the issues identified in the Opinions, this was not the case. The Opinions were obviously quoted by the European Communities as evidence of the insufficiencies it has identified in its Opinions. However, the European Communities, while stating that the Opinions identified relevant issues, basically left it to the Panel to find out on its own the relevance of certain issues identified in the quotations for the question whether relevant scientific evidence was insufficient or not.[737]

7.636 The Panel is therefore of the view that, in light of its functions under the DSU, it should limit its review of alleged insufficiencies in the relevant scientific evidence to those specifically discussed by the European Communities in its submissions. It will only address the issues identified in the Opinions to the extent they are sufficiently related to an issue *discussed* by the European Communities.

7.637 A second question relates to the fact that, even when a particular insufficiency was specifically discussed by the European Communities, elements were not always available to address this insufficiency on a hormone-specific basis. The arguments and generally the information presented to the Panel were not always specific enough to permit this. In spite of our repeated

[734] We have already explained in para. 7.578 why we do not believe that abuse or misuse is an issue of insufficiency of relevant evidence.

[735] See EC's reply to questions 22 and 30 of the questions of the Panel after its first substantive meeting, Annex B-1, and part 2, Section II.B and Section III.C of the EC's second written submission.

[736] See Appellate Body Report in *Canada – Wheat Exports and Grain Imports*, para. 191.

[737] See Appellate Body Report on *US – Gambling*, para. 140.

requests, several questions were addressed by the parties or the experts in general terms, rather than specifically for each of the five hormones, thus making an assessment of particular issues hormone-by-hormone sometimes impossible.

7.638 Under the circumstances, the Panel decided:

(a) first, to address the insufficiencies *as identified and discussed* by the European Communities in its arguments and only to the extent evidence had been submitted by the parties in relation to them. This approach is, in our opinion, consistent with the requirement identified by the Appellate Body in its report on *Japan – Agricultural Products II* that panels refrain from "making a case" for one party in the absence of a prima facie case by that party;[738]

(b) second, to address some concerns aggregately for all of the five hormones at issue, to the extent that information was not submitted on an hormone-specific basis, or to the extent an issue was raised with respect to all hormones, but evidence submitted only for one or two of them; and

(c) third, to address individually for each hormone the issues for which specific information on that hormone was provided to the Panel.

7.639 For these reasons, we have decided to address first, in a "common issues" section, the insufficiencies which were not addressed by the parties and the experts in a hormone-specific manner (i.e. those for which arguments or evidence were not hormone-specific), or which were not addressed specifically enough to justify a separate analysis for each of the hormones concerned. At a second stage, we address for each hormone the alleged insufficiencies which have been discussed in relation to that hormone and for which arguments and evidence were specifically provided.

(vi) Issues common to all five hormones for which evidence was not provided on a hormone-specific basis

Introduction

7.640 We note that, despite our insistence that information be provided for each of the five hormones at issue, arguments, information and opinions have sometimes addressed all or part of the scientific evidence on these hormones together. As a result, in this section, we will address the issues that were specifically discussed by the European Communities in these proceedings in relation to all five hormones in general regarding their use as growth promoters in cattle. More particularly, we will address:

(a) the effects of hormones on certain categories of population, such as pre-pubertal children;

(b) dose response;

(c) bioavailability;

(d) the EC claim that the long latency period of cancer makes it more difficult to demonstrate insufficiency of the relevant evidence regarding the carcinogenicity of the hormones at issue;

[738] See Appellate Body Report on *Japan – Agricultural Products II*, para. 129.

(e) the impact of the five hormones at issue on the immune system; and

(f) the impact of the five hormones at issue on development and reproduction.

Effects of hormones on certain categories of population

7.641 Regarding the effect of the hormones at issue on certain categories of populations, we note that the European Communities refers to the conclusions contained in the Opinions. We recall that the 1999 Opinion mentions that prepubertal and postmenopausal women and prepubertal and adult men have the lowest levels of endogenous oestrogens and progesterone and thus would represent the individuals most likely to be at increased risk for the adverse health effects that might be associated with exposure to exogenous sources of oestrogens. Likewise, the 1999 Opinion provides that all women and prepubertal men represent the individuals at greatest risk for adverse health effects that might be associated with exposure to exogenous sources of testosterone.

7.642 The 1999 Opinion specifies that the hormone levels on which it relies were determined by radio-immunoassays (RIA) and that the use of these assays has frequently been associated with production of variable results, particularly when used to detect low levels of endogenous hormones. The 1999 Opinion notes that Klein et al. (1994) developed an ultrasensitive assay (100-fold more sensitive than RIAs) which identified values of oestradiol considerably lower than the range of oestradiol levels found through RIAs for prepubertal children. The 1999 Opinion concludes that "[a] corollary is that perhaps the hormones residues in beef, which are also low and which have been determined by RIA are equally variable and over representative of the actual hormones concentration." The 1999 Opinion concludes that this is a critical area requiring additional study.[739]

7.643 We recall our test regarding insufficiency of relevant evidence in this case, i.e. that there must be a critical mass of new evidence and/or information that calls into question the fundamental precepts of knowledge and evidence so as to make relevant, previously sufficient, evidence now insufficient. In that context, we believe that the question before us is whether the more sensitive detection methods which identified lower hormonal levels in pre-pubertal children than thought until now are such as to call into question the range of physiological levels of the sex hormones in humans currently believed to exist.

7.644 Dr. Sippell specified that:

> "There is no doubt that the development of an ultrasensitive recombinant cell bioassay (RCBA) of E_2 by Karen Klein, Gordon Cutler and co-workers at the N.I.H. in Bethesda, USA (Klein et al 1994) represented a quantum leap in E_2 assay methodology. It opened a new door on our understanding of basic physiological phenomena, e.g. why normal puberty starts so much earlier in girls than in boys or why bone maturation in children differs so much between the sexes. The validity of the N.I.H.-RCBA has now been confirmed by another RCBA of E_2 which was developed by Charles Sultan's group at the University of Montpellier, France (Paris et al 2002). Unfortunately, the complexity of the RCBA so far prevents its wider use

[739] The 2002 Opinion refers to a new method to detect trace amounts of hormones in meats and to three complementary bioassays involving different recombinant-DNA technology for screening and determination of oestrogenic potency of substances used as growth promoters (2002 Opinion, p. 9). The Panel nonetheless understands that these method and bioassays address a different issue than the identification of endogenous levels of hormones in humans.

> for routine measurements in small serum samples from infants and prepubertal children."[740]

7.645 We also note Dr. Sippell's statement that "[t]he risk to children arising from hormones which are naturally present in meat as compared to that from residues of hormonal growth promoters has, to my knowledge, been estimated for E_2 [i.e. oestradiol-17β] only and only in beef (Daxenberger et al. 2001)."[741]

7.646 We recall the statement of the 2000 Opinion referring to novel techniques in chemical analysis[742] but mentioned that "additional time will be required to validate and apply this methodology in a reliable, accepted fashion before a re-evaluation of this issue can be conducted."[743] This opinion is confirmed by Dr. Boobis.[744] Dr. Boobis expressed additional concerns about the validity of the Klein et al. (1994) study:

> "There is certainly some evidence that endogenous levels of hormones in children are lower than previously thought. However, the suggestion that this is by orders of magnitude is not substantiated by the data. One group has reported very low levels of oestradiol in male children, 0.08 pg/ml *(Klein et al, 1994)*, but in a later study *(Klein et al, 1998)*, the same group reported mean levels somewhat higher, at 0.27 pg/ml. The reliability of the Klein et al assay has yet to be determined. The assay is particularly sensitive to oestradiol, but there is no obvious explanation for this, as it relies upon affinity for the oestrogen receptor. Diethylstilbestrol is a potent oestrogen yet is much less sensitive than oestradiol in the assay. *Klein et al (1994)* have reported that there are unidentified factors in plasma and in blood collection tubes that can interfere in the assay. In contrast, using a similar yeast-based assay, *Coldham et al (1997)* found that oestradiol and DES had similar potency, and others have found that, if anything, DES is more potent than oestradiol in such assays *(Folmer et al, 2002)*. At the very least, this shows that results with the yeast reporter assay are not consistent, and use of such data in risk assessment requires that the assay be adequately validated.[745]
>
> However, there are studies from two other groups using more specific methods than the original radioimmunoassay, reporting that levels were somewhat higher than this. *Ikegami et al (2001)* used a very sensitive, 2-stage immunoassay technique. This was

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[740] Reply of Dr. Sippell to question 40 of the Panel, Annex D, para. 328.

[741] Reply of Dr. Sippell to question 41 of the Panel, Annex D, para. 335.

[742] Results of "hormone" residue analyses of bovine meat and liver imported into the EU and originating from the USA "Hormone Free Cattle Program" analysis – First Interim Report, May 1999 – R.W. Stephany and F. André (rapporteurs).

[743] 2000 Opinion, p. 3.

[744] Transcript of the Panel meeting with the experts, Annex G, para. 572.

[745] Dr. Boobis' reply to question 40 of the Panel, Annex D, para. 324. Dr. Boobis cites to:

> Coldham NG, Dave M, Sivapathasundaram S, McDonnell DP, Connor C and Sauer MJ (1997). Evaluation of a recombinant yeast cell estrogen screening assay. Environ Health Perspect, **105**:734-742
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> Folmar LC, Hemmer MJ, Denslow ND, Kroll K, Chen J, Cheek A, Richman H, Meredith H and Grau EG (2002). A comparison of the estrogenic potencies of estradiol, ethynylestradiol, diethylstilbestrol, nonylphenol and methoxychlor in vivo and in vitro. Aquat Toxicol, **60**:101-110
>
> Klein KO, Baron J, Colli MJ, McDonnell DP and Cutler GB Jr (1994). Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. J Clin Invest, **94**:2475-2480
>
> Klein KO, Baron J, Barnes KM, Pescovitz OH and Cutler GB Jr (1998). Use of an ultrasensitive recombinant cell bioassay to determine estrogen levels in girls with precocious puberty treated with a luteinizing hormone-releasing hormone agonist. J Clin Endocrinol Metab, **83**:2387-2389

shown to be specific and sensitive. In this assay, mean levels of oestradiol in prepubertal males were 1.85 pg/ml (6.8 pmol/ml). *Paris et al (2002)* used a recombinant oestrogen receptor assay in a mammalian cell line, a similar principle to the assay of Klein et al. In this study, estrogenic levels in prepubertal males were found to be 1.44 pg/ml. There are many issues affecting such measurements. These include the presence of binding proteins, relative specificity and sensitivity. None of the assays is entirely specific for oestradiol. Both the oestrogen receptor and the antibodies used could cross-react with structurally relayed compounds. Depending on how the assay is performed, protein binding could reduce the concentration of hormone detectable in the assay by sequestering hormone from the assay target. However, it should be noted that whilst binding to protein in plasma my reduce clearance it will also reduce the biologically active dose. In general, it is the free concentration that determines biological activity *(Teeguarden and Barton, 2004)*. Hence, if SHBG is elevated in children this would tend to reduce the effect of an equivalent total plasma concentration by reducing the free concentration.

The advantage of the recombinant assays is that they measure biologically active material, whereas the immunoassays may include cross-reacting less or inactive metabolites. Whilst the recombinant assays may include hormonally active material other than the specific analyte, this does provide an indication of to what the body is exposed in vivo. Hence, on balance, the data of *Paris et al (2002)* may be the most meaningful to date. This presumably reflects circulating total active oestrogenic material, but not that bound to proteins."[746]

7.647 We note that the evidence presented relates only to oestradiol, but that the claim we are examining with regard to the insufficiencies of the evidence are with respect to the five other hormones at issue, not oestradiol. We note furthermore that the 2002 Opinion concludes that these more sensitive detection methods have not yet been validated.[747]

7.648 On the basis of the above, we are not convinced that the studies discussed by the experts call into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient evidence now insufficient in relation to the effect of the five hormones on pre-pubertal children. Particularly, it has not been established that the data regarding the effects of hormones on which the JECFA assessments are based are insufficient in light of new evidence relating to the other five hormones at issue.

[746] Reply of Dr. Boobis to question 40 of the Panel, Annex D, paras. 325-326. Dr. Boobis cites to:

Ikegami S, Moriwake T, Tanaka H, Inoue M, Kubo T, Suzuki S, Kanzakili S and Seino Y (2001). An ultrasensitive assay revealed age-related changes in serum oestradiol at low concentrations in both sexes from infancy to puberty. Clin Endocrinol (Oxf), **55**:789-795
Paris F, Servant N, Terouanne B, Balaguer P, Nicolas JC and Sultan C (2002). A new recombinant cell bioassay for ultrasensitive determination of serum estrogenic bioactivity in children. J Clin Endocrinol Metab, **87**:791-797
Teeguarden JG and Barton HA (2004). Computational modeling of serum-binding proteins and clearance in extrapolations across life stages and species for endocrine active compounds. Risk Anal, **24**:751-770

[747] 2002 Opinion, Section 4.1.1, p. 9.

Dose response

7.649 The European Communities, in its reply to a question of the Panel[748], quotes an extract of the 1999 Opinion.[749] Whereas this quotation relates to trenbolone acetate, we decided to address it in this general section to the extent that the impossibility to perform a dose-response assessment is referred to by the European Communities with respect to the five hormones at issue.[750]

7.650 The European Communities also questions JECFA's findings on dose response as follows:

> "The above findings establish that the levels of endogenous production of these hormones by **pre-pubertal children** is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship, because the data on endogenous production on which JECFA based its findings are also very old (since 1974)."[751]

7.651 The Panel can only conclude from the comments of the European Communities that it considers that a dose response would be required to complete a risk assessment for the five hormones other than oestradiol-17β, but that it disagrees with JECFA's findings on dose response. The Panel notes that JECFA could identify a dose response for the five hormones at issue. Comparatively, the European Communities has not provided convincing elements to support its view that there is insufficient relevant evidence on dose response. The EC position on dose response, at least for the natural hormones other than oestradiol, seems to be based on the belief that levels of endogenous production of hormones are much lower than previously thought. The Panel notes in this regard that it has been demonstrated that the ultrasensitive assay relied upon by the European Communities to conclude that endogenous production is lower than assumed by JECFA has not yet been validated and applies only to oestradiol.

7.652 For these reasons, the Panel believes that it has not been established that new evidence was such as to put into question existing data on dose response and prevent the performance of a risk assessment.

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[748] EC's replies to Panel questions after the first substantive meeting, question 22, Annex B-1.
[749] 1999 Opinion, para. 4.4.8.
[750] See the following paragraphs of the EC's second written submission:
- para. 150, regarding the effect of progesterone on growth and reproduction: "No assessment of the dose response relationship has been presented yet." Also: "In conclusion, these data indicate that progesterone can cause immuno depression; however, they are insufficient to make any realistic assessment of the dose response relationship." (Both from the 1999 Opinion, pp. 51-55);
- para. 153, regarding the effect of testosterone on growth and reproduction: "No assessment of the dose response relationship has been presented yet." Also: "There are limited experimental data on the effects of testosterone on immuno response but none on the dose response aspects." (Both from the 1999 Opinion, p. 50);
- para. 156, regarding the effects of trenbolone on growth and reproduction: "These data do not allow a realistic assessment of a dose response relationship." (1999 Opinion, p. 60);
- para. 161, regarding melengestrol acetate: "These data do not allow an estimate of the dose response relationship." (1999 Opinion, p. 68);
- para. 158, on the effects of zeranol on growth and reproduction: "No estimate of the dose-response relationship for these effects can be made."(1999 Opinion, p. 65).

[751] EC's second written submission, para. 104.

Bioavailability

7.653 The European Communities argues that another area where recent developments put in doubt the findings of the 1999 JECFA report concerns the bioavailability of residues of the hormones concerned. According to the European Communities, the 1999 and 2002 Opinions have found that data on which JECFA based its findings are incorrect or insufficient.[752]

7.654 The Panel notes that the studies referred to in the 1999 and 2002 Opinions (one of them being study 3 of the 17 studies commissioned by the European Communities)[753] relate to oestradiol-17β, not to any of the specific hormones with respect to which the European Communities applies a provisional ban under Article 5.7 of the *SPS Agreement*. Moreover, there is no indication that the conclusions can be applied to other hormones than oestrogens.

7.655 The Panel recalls that the European Communities argued that "similar findings [had been] made for all of the other five hormones."[754] However, the European Communities did not specify where such findings had been made. The European Communities also refers to study 10 of the 17 studies, by Dr. Florence Le Gac, but does not clearly explain to what extent the results of this study establish or discuss the bioavailability of the five other hormones. This allegation of the European Communities has to be considered in light of the statements of Dr. Boisseau and Dr. Boobis according to which the bioavailability of melengestrol, trenbolone and zeranol residues has not been determined.[755]

7.656 The Panel considers that bioavailabity would be an issue if the new evidence suggested that bioavailability in the case of ingestion of meat treated for growth promotion purposes is higher than previously thought. However, it appears that, in the absence of data, JECFA assumed 100% bioavailability.

7.657 In this respect, Dr. Boisseau said:

> "The bioavailability of melengestrol, trenbolone and zeranol residues have not been determined. Therefore all their residues have been considered as being totally bioavailable."[756]

7.658 Dr. Boobis stated, with respect to natural hormones, that "change in bioavailability is likely to be a consequence of changes in the enzymes of metabolism in the liver and/or small intestine."[757]

7.659 Dr. Boobis also confirms for the non-natural hormones:

> "However, it should be noted that in the risk assessment of these hormones by JECFA, the risk characterization involved comparison of the theoretical maximum daily intake with the ADI. No correction was made for bioavailability. Hence, the situation is likely to be similar to that for the natural hormones, in that changes in bioavailability from the normal value would change the margin of safety."[758]

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[752] EC's second written submission, para. 105.

[753] 2002 Opinion p. 12, point 4.1.5, Exhibit CDA-7; Study 3: "Estrogenic activity of oestradiol and its metabolites in the ER- CALUX assay with human T47D breast cells", APMIS 109: 101-7, 2001. Exhibit EC-9.

[754] EC's reply to question 28 of the questions of the Panel after the first substantive meeting, Annex B-1, para. 158.

[755] Dr. Boisseau, Annex D, para. 347.

[756] Annex D, para. 347.

[757] Annex D, para. 350.

[758] Annex D, para. 351.

7.660 These statements were not contradicted by Dr. Guttenplan, the third and last expert who replied to question 43 of the Panel, and who limited his remarks to oestrogens.[759]

7.661 We therefore conclude that it has not been established that any new evidence on bioavailability has been developed regarding specifically the five hormones at issue, which would affect the current knowledge on the subject. More particularly, no new evidence has been submitted regarding the three non-natural hormones which would make it impossible to perform a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*.

Long latency period of cancer and confounding factors

7.662 Regarding the long latency of cancer, in its second written submission[760], the European Communities claims that it may not be in a position to demonstrate the existence of a clear harm in case of cancer because of the long latency period and the numerous confounding factors that play a role in the development of cancer.

7.663 We first note the importance of latency period in the assessment of cancer, as confirmed by Dr. Cogliano, Dr. Guttenplan and Dr. Boobis:

7.664 Dr. Cogliano stated that:

> "It is definitely necessary to take into account the latency period of cancer in the conduct of a risk assessment. In this regard, the guidelines for developing *IARC Monographs* state, 'Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.' [International Agency for Research on Cancer, Preamble to the *IARC Monographs*, http://monographs.iarc.fr]"[761]

7.665 Dr. Guttenplan confirmed that:

> "When epidemiological data is used in performing a risk assessment, the latency period is extremely important. Usually a latent period of 20 years is taken for cancer, but this varies with the carcinogen. It is indeed necessary to determine incidence or prevalence at different times after the onset of exposure. Attempting to perform a risk assessment based on epidemiological data obtained too soon after the onset of exposure can seriously underestimate risk."[762]

7.666 Dr. Boobis stated that:

> "The latency period is an important consideration in risk assessment, both in the design and in the interpretation of studies. Thus, the duration of exposure, either of experimental animals or in epidemiology studies, should be sufficiently long to permit assessment of effects with a long latency period. Most forms of cancer come into this category."[763]

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[759] Annex D, para. 357.
[760] EC's second written submission, para. 143.
[761] Reply of Dr. Cogliano to question 23 of the Panel, Annex D, para. 213.
[762] Reply of Dr. Guttenplan to question 23 of the Panel, Annex D, para. 214. Dr. Guttenplan cited to Lagiou P. Trichopoulou A. Trichopoulos D. Nutritional epidemiology of cancer: accomplishments and prospects. [Lectures] Proceedings of the Nutrition Society. 61(2):217-22, 2002.
[763] Reply of Dr. Boobis to question 23 of the Panel, Annex D, para. 210.

7.667 Dr. Boobis added that:

> "The observational studies of humans (e.g. on HRT or oral contraceptives) and the experimental studies in animals covered a sufficiently long period to encompass the latency period for any carcinogenic effects of the hormones (see *IARC, 1999)*.

7.668 Dr. Boisseau highlighted the practical difficulties resulting from confounding factors, arguing that:

> "[He did] not think possible/useful to take into account the "long latency period" of cancer in order to assess properly and specifically the carcinogenic effects of residues of natural hormones only resulting from the treatment of food producing animals by growth promoting hormones. ... epidemiological studies carried out in humans during [periods] long enough in order to take into account this "long latency period" will not be able to discriminate, in the case of a possible but limited increase of tumours, between the responsibilities of (1) hormone residues resulting from the treatment of food producing animals by growth promoting hormones, (2) hormone residues resulting from the endogenous production of these animals, (3) other components of the diet including other food additives and contaminants. That is the reason for which, ... the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters."[764]

7.669 Dr. Boobis added that:

> "The long term studies of the hormones undertaken in experimental animals and in humans, involved much higher doses than would be encountered on consumption of meat from animals treated with growth promoting hormones. The maximum risk from such low levels of exposure, even assuming a linear dose-response relationship for cancer, would be such that it would be necessary to study extremely large populations to detect any increase in cancer incidence, particularly as the most likely cancers are quite common. This is because the lower the risk the greater the number of subjects that are required to detect it, a function of the power of the study which takes account the magnitude of the risk and the difference from the background rate *(Hunter, 1997)*. Hence, in the risk assessment of the hormones used as growth promoters, it is questionable whether an increase in risk, even if it existed, could be detected in exposed populations. However, it is still necessary to protect against such a risk. The risk assessment of the hormones conducted by JECFA suggested that there would be no risk at exposure levels up to the respective ADI. Even if duration of exposure were for a sufficiently long period (usually 20-25 years for solid tissue tumours), any increase in risk would probably not be detectable. Hence, a negative result from such an observational study would not resolve the issue.
>
> A second issue with respect to the latency is the significance it has for interpretation of the exposure pattern. Where there is a long latency, and regular exposure is necessary before a carcinogenic response is manifest, as appears to be the case for the hormones in question *(Coombs et al, 2005)*, occasional exposures above the ADI will

[764] Reply of Dr. Boisseau to question 23 of the Panel, Annex D, para. 209.

> not pose any additional risk *(Larsen and Richold, 1999)*. Hence, latency is of value in assessing the risks from different exposure scenarios."[765]

7.670 The European Communities acknowledges that epidemiological studies will not be able to discriminate (or separate out) the true origin of cancer because of so many confounding factors. In this respect, we note that Dr. Cogliano specified that it was generally possible to identify confounding factors in epidemiological studies. It was often difficult, however, to determine whether the observed tumours can be attributed to the agent under study or to a confounding factor. Dr. Cogliano adds that "[w]hen a causal interpretation is credible but confounding factors cannot be ruled out, IARC considers this to provide *limited evidence of carcinogenicity*."[766]

7.671 The European Communities insists, however, that this undermines the opinion of the respondent that the hormones at issue have been in use for a sufficiently long time to rule out their carcinogenic effect on humans. The European Communities points at IARC studies showing that the frequency of breast cancer in countries where use of hormones for growth promotion is allowed is higher compared with countries where the hormones have not been used.[767]

7.672 Three experts addressed this issue. Dr. Cogliano mentioned that:

> "The difference between the US and the EC in rates of breast cancer and prostate cancer almost certainly has multiple causes. It is possible that differences in exposure to exogenous hormones can be one cause, but the data are not sufficiently specific to establish a link between these observations."[768]

7.673 Dr. Guttenplan confirmed that:

> "The epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters. The references to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities are not very convincing as there is considerable variation in rates in different geographical locations. Also, the differences in rates of breast and prostate cancer observed in the United States as compared to the European Communities are relatively small. There is no way to definitely establish a link between these statistics and the consumption of meat from animals treated with the hormones at issue as there are many possible confounders, and the differences in cancer rates are small.

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[765] Dr. Boobis cites to the following studies:

Coombs NJ, Taylor R, Wilcken N, Fiorica J and Boyages J (2005). Hormone replacement therapy and breast cancer risk in California. Breast J, 11:410-415
Hunter DJ (1997). Methodological issues in the use of biological markers in cancer epidemiology: cohort studies. IARC Sci Publ, **142**:39-46
IARC (1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 72. Hormonal Contraception and Post-menopausal Hormonal Therapy, IARC, Lyon, France
Larsen JC and Richold M (199). Report of workshop on the significance of excursions of intake above the ADI. Regul Toxicol Pharmacol, **30**:S2-12.
See Reply of Dr. Boobis to question 23 of the Panel, Annex D, para.212.

[766] Reply of Dr. Cogliano to question 24 of the Panel, Annex D, para.220. See also Dr. Guttenplan, Annex D, para.221.

[767] EC's comments on experts' replies to questions 23 and 24 of the Panel, Annex F-1, pp. 19-20.

[768] Reply of Dr. Cogliano to question 26 of the Panel, Annex D, para. 241.

However, the results are at least consistent with a possible effect of hormones on breast and prostate cancer."[769]

7.674 In this regard, Dr. Boobis added the following:

"There are an appreciable number of studies showing an association between the risk of certain cancer types, including breast and prostate and the consumption of meat *(Colli and Colli, 2006; Norat et al, 2005; see also SCVPH Opinion, 1999)*. For breast, the incidence is similar in developed countries such as Western Europe, North America and Australasia. The correlation is strongest with meat consumption and shows little relationship with whether the meat is from animals treated with growth promoting hormones or not. For example rates in Iceland (87.2 per 100,000), where such hormones are not used, are not dissimilar to those in the USA (101.1 per 100,000), where they are used. Prostate cancer rates are 124.8/100,000 in the USA and 90.9 per 100,000 in Sweden *(IARC, 2002)*. For comparison, average daily consumption of meat (as protein) in 2000 was as follows: USA 40.2 g/day; Iceland 29.5 g/day; Sweden 24.8 g/day *(FAO, 2003)*. Hence, there is a much better association with meat consumption and risk of breast or prostate cancer than there is with the use of growth promoting hormones to treat cattle. It is also important not to infer too much from geographical differences in cancer incidence rates with respect to causation. This is because of what is known as the ecological fallacy. This has been defined as the inference that a correlation between variables derived from data grouped in social or other aggregates (ecological units) will hold between persons (individual units) *(Society for Risk Assessment, 2004)*. The difficulty is that many factors will vary between populations, including ethnicity, genetics, health and socioeconomic status, diet, lifestyle and environment. Without considering the possibility of confounding, such ecological data is really only of value in generating hypotheses *(Morgenstern, 1995)*. These would need to be evaluated in more structured investigations, with better control of confounding variables."[770]

7.675 We also note Dr. Boobis statement at the meeting of the Panel with the experts:

"The paradigm we have, and there is some evidence to justify the case that this is a reasonable assumption, is that the effects observed scale to the lifetime of the organism, and so that is one of the reasons we use shorter-lived organisms in our toxicological testing. We use rats and mice which live for a couple of years; otherwise we would have to test for a lifetime in a longer-lived species which might be 40 or 50 years. So we are working on the principle that effects that are not evident within the lifetime of a rodent would not be evident, all other things being equal, within the lifetime of a human being. And there is actually very good evidence that that is the case. For a number of carcinogens that IARC have evaluated it takes approximately a quarter of a lifetime after an initial exposure for those tumours to become apparent, and that is true in rodents, it's true in dogs and it's true in humans. So I think that the paradigm is reasonable that if there is going to be an effect

[769] Reply of Dr. Guttenplan to question 26 of the Panel, Annex D, para. 242.

[770] Reply of Dr. Boobis to question 26 of the Panel, Annex D, para. 239. Dr. Boobis cited to the following:

Morgenstern H (1995). Ecologic studies in epidemiology: concepts, principles, and methods. Annu Rev Public Health, 16:61-81

Society for Risk Assessment (2004). Glossary of Risk Analysis Terms. (http://www.sra.org/resources_glossary.php)

> manifest over a lifetime, it will be revealed in those experimental systems and therefore be predictive of lifetime effects in humans by and large."[771]

7.676 On the one hand, the comments of the experts suggest that epidemiological studies have not been able to single out residues of hormones in meat treated for growth promotion purposes as a cause of cancer, and that this would be quite difficult. On the other hand, the Panel notes that it is possible to assess long term effects through long term studies of experimental animals, even if they involve much higher doses than would be encountered in consumption of meat from animals treated with growth promoting hormones. It has also been possible to take into account the risk attached to latency through the setting of ADI. The European Communities has not identified any evidence quantitatively and qualitatively sufficient to call into question the fundamental precepts of existing knowledge and evidence and the approach followed so far in order to integrate the long latency of cancer in risk assessment.

7.677 Having regard to the opinions of the experts, the Panel concludes that it has not been established that the difficulties attached to the long latency of cancer make it impossible to perform a risk assessment within the meaning of Article 5.1 and Annex A(4) of the *SPS Agreement*. More particularly, the European Communities did not point at a "critical mass" of new evidence and/or information that would call into question the fundamental precepts of previous knowledge and evidence in relation to the long latency period of cancer and the existence of confounding factors.

Effect of hormones on the immune system

7.678 The 1999 Opinion considers, for each of the five hormones for which a provisional ban is applied, that there is insufficient evidence as to their effect on the immune system.[772] The Panel notes that no arguments have been raised specifically in relation to the effects of hormones on the immune system with respect to each of the five hormones at issue. The Panel noted, however, the contention of the European Communities that new important gaps, insufficiencies and contradictions had been identified in the scientific information and knowledge now available as a result of the 17 studies commissioned by the European Communities. The Panel considered that an appropriate way to address this question with respect, *inter alia*, to the effect of hormones on the immune system was to seek the views of the scientific experts on the factual question whether the new scientific studies initiated since 1997 and relied upon by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue.[773]

7.679 Three experts expressed their views on the matter. Dr. Boobis argued that:

> "The evidence on immune effects of hormones such as oestradiol referred to by the EC does not identify any adverse effects on the immune system from consumption of meat from treated cattle. In general, clear evidence for immune effects were observed only at high doses. There is no evidence that doses such as those resulting from consumption of meat from treated animals has any effect on the immune system *(*JECFA*, 2000b; CVMP, 1999).* It should also be noted, that in the case of immune effects, exposure relative to endogenous levels is a critical issue. Given the large margin of exposure on anticipated intake from residues in meat from treated animals,

[771] Annex G, para. 1031.
[772] There does not seem to be any additional development on this matter in the 2000 and 2002 Opinions.
[773] Question 59 of the Panel to the experts.

> no effect on the immune system is anticipated, as immune modulation is dependent on dose and there are thresholds for such effects."[774]

7.680 Dr. Guttenplan noted that:

> "The relationship between estrogen and autoimmune diseases has received considerable attention (Opinion SCVPH, April 30, 1999, section 2.4). There is evidence that estrogens can be involved in Lupus, rheumatoid arthritis, thyroiditis. In addition the development of allergies is thought to be at least partially related to estrogens. The studies in experimental animals also did not identify any immune-related effects, although it is not certain the types of possible effects in humans would be detected in experimental animals. No definitive studies have related intake of meat from hormone-treated animals to the above disorders."[775]

7.681 We note that the Panel question related to all hormones and the experts gave details in relation to oestrogens in general. We also note that the European Communities, in its comments on the experts replies, referred to effects identified by Dr. Guttenplan in relation to oestrogens. The European Communities concludes that it has offered serious evidence and pointed to a number of gaps and uncertainties in the knowledge. The European Communities considers that it is for the United States, Canada and JECFA to "ensure the Panel that adverse immune effects are not possible to occur from residues in meat treated with these hormones for animal growth promotion".[776]

7.682 First, the Panel doubts that, in this particular case, the standard of proof is that Canada should prove to the satisfaction of the Panel that "adverse immune effects are not possible to occur from residues in meat treated with these hormones for animal growth promotion" purposes. As already specified, in this case Canada has to prove its allegation that relevant scientific evidence is not insufficient to perform an adequate risk assessment under Article 5.1 and Annex A(4) of the *SPS Agreement*.

7.683 Second, with regard to the evidence and gaps allegedly identified by the European Communities, the Panel notes that the statement of Dr. Guttenplan on which the European Communities relies relates exclusively to oestrogens. The Panel notes in this respect that the other experts' replies to question 59 of the Panel relate to oestradiol or oestrogens. None of those replies related to any of the five hormones at issue. The Panel notes that the 1999 Opinion itself does not provide evidence of impact on the immune system for testosterone.[777] For progesterone, the data were deemed to indicate that progesterone can cause immuno depression. However they were described as insufficient to make a realistic assessment of the dose response relationship.[778] On trenbolone, the information was deemed insufficient to assess the possible impact of low levels of trenbolone in meat and meat products on consumers.[779] For zeranol, the 1999 Opinion states that no relevant data on the

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[774] Reply of Dr. Boobis to question 59 of the Panel, Annex D, para. 445. Dr. Boobis cited to:

Barton HA and Clewell HJ 3rd (2000). Evaluating noncancer effects of trichloroethylene: dosimetry, mode of action, and risk assessment. Environ Health Perspect, 108 (Suppl 2):323-334
Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG and Wurtzen G; European branch of the International Life Sciences Institute (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol, **42**:65-83

[775] Reply of Dr. Guttenplan to question 59 of the Panel, Annex D, para. 447.
[776] EC's comments to experts' replies to Panel questions, Annex F-1, pp. 37-38.
[777] 1999 Opinion, p. 51.
[778] 1999 Opinion, p. 55.
[779] 1999 Opinion, p. 60.

effect of zeranol on the immune system were found.[780] Finally, for MGA, the 1999 Opinion concluded that the information was insufficient to make a scientific judgement on whether MGA may cause effects on the immune system at a level which could occur in meat treated with MGA as a growth promoters. The 2000 and 2002 Opinions do not seem to contradict these findings.

7.684 The Panel also notes that the three experts who replied to question 59 addressed the potential effects of hormones on the immune system through a dose-response approach.[781] The Panel has received no evidence suggesting that a dose response would not apply to the effect of the five hormones on the immune system as a result of the consumption of meat treated for growth promotion purposes.

7.685 We therefore conclude that it is not established that there exists a critical mass of new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient, evidence on hormones effects on the immune system now insufficient.

Effect of hormones on growth and reproduction

7.686 The Panel notes that no arguments have been raised specifically in relation to growth and reproduction with respect to each of the five hormones at issue, except for the EC reference to the 1999 Opinion. The Panel notes, however, the contention of the European Communities that new important gaps, insufficiencies and contradictions had been identified in the scientific information and knowledge now available as a result of the 17 studies commissioned by the European Communities. The Panel considers that an appropriate way to address this question with respect, *inter alia*, to the effect of hormones on growth and reproduction was to seek the views of the scientific experts on the factual question whether the new scientific studies initiated since 1997 and relied upon by the European Communities actually support its contention.[782]

7.687 Three experts commented on our question, Dr. Boisseau, Dr. Boobis and Dr. Guttenplan. Only Dr. Boobis and Dr. Guttenplan discussed matters related to growth and reproduction. Dr. Guttenplan originally identified a number of gaps that could relate to growth and reproduction.[783] However, Dr. Guttenplan subsequently stated that "on subsequent reading, [he] could not find anything to indicate adverse effect", and he considered that it was possible to undertake a risk assessment.[784] He added that "the ability [to make a risk assessment] varies between compounds, but that does not mean you can't make a risk assessment, it just means the accuracy of the risk assessment is different."[785]

7.688 Dr. Boobis considered in general that:

> "[T]here is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat from treated animals can be assessed. Whilst additional information has been obtained on a number of aspects of the hormones in question, this was often not definitive, sometimes it was not relevant, in some instances it

[780] 1999 Opinion, p. 66.
[781] See also reply of Dr. Boissau to question 59 of the Panel, Annex D, para. 443.
[782] See question 62 of the Panel to the scientific experts, Annex D.
[783] Reply of Dr. Guttenplan to Question 62 of the Panel, Annex D, paras. 497-499.
[784] Transcript of the Panel meeting with the experts, Annex G, para. 981.
[785] Transcript of the Panel meeting with the experts, Annex G, para. 983.

> confirmed or expanded on previous knowledge. The evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion."[786]

7.689 Dr. Boobis also discussed the recent data on endocrine and developmental effects of the hormones at issue. Regarding the experimental studies on the effect of in utero exposure of rabbits to the three exogenous hormones: melengestrol acetate, trenbolone acetate and zeranol, also referred to in the 2002 Opinion (study 11), Dr. Boobis noted that, to date, only information on metabolism and disposition had been published *(Lange et al, 2002)*.[787] According to Dr. Boobis:

> "[the Lange et al. paper (2002)][788] demonstrates transplacental transfer of the three hormones. This is not surprising given the physicochemical properties of the compounds (lipid solubility, non-polar, molecular size) *(Syme et al, 2004)*.[789] In addition, endogenous hormones are known to cross the placenta. It is notable that in the study of Lange et al, fetal concentrations of the hormones and their metabolites were similar to or less than, sometimes much less than, those in corresponding maternal tissues, suggesting that there was no net accumulation of the compounds in fetal tissues. It is also noted that the number of animals studied was very small, a point commented on by the authors themselves.
>
> The unpublished component of this study was an investigation of the potential health consequences of in utero exposure of rabbits to the three hormones. From the information provided, low dose exposure in utero caused modest changes in some parameters, but was not associated with wither cancer or adverse effects on reproductive capacity. There were no changes in sperm number. It is not clear whether the changes observed were consistent and hence compound-related as a only a single dose was used for each compound. Nor is it apparent whether the magnitude of all of changes discussed reached statistical significance (often the changes were described as slight and no measure of variance is provided). The doses used in this study would have provided much higher levels of exposure than those predicted to arise from residues in meat. In the case of trenbolone acetate and zeranol exposure was via the subcutaneous route, thus bypassing presystemic metabolism in the intestine and/or the liver. In the case of MGA the oral dose was over 16,500 times the ADI. Hence, even if the effects observed were of toxicological significance the ADI would provide a more than adequate margin of protection.
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> Overall, this study cannot be said to confirm a risk to human health from consumption of meat from animals treated with these hormones."[790]

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[786] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 495.

[787] Dr. Boobis noted that, given the time that had elapsed since this paper was published (submitted September 2001), it was somewhat surprising the data from the remainder of the study had not been published yet.

[788] Dr. Boobis cited to Lange IG, Daxenberger A, Meyer HH, Rajpert-De Meyts E, Skakkebaek NE and Veeramachaneni DN (2002). Quantitative assessment of foetal exposure to trenbolone acetate, zeranol and melengestrol acetate, following maternal dosing in rabbits. Xenobiotica, **32**:641-651 See Reply of Dr. Boobis to question 63 of the Panel, Annex D, paras. 488-490.

[789] Dr. Boobis cites to Syme MR, Paxton JW and Keelan JA (2004). Drug transfer and metabolism by the human placenta. Clin Pharmacokinet, 43:487-514. Ibid.

[790] Dr. Boobis also discussed the study called "Retrospective study on long-term effects in children of following suspected exposure to oestrogen-contaminated meat" (study 12) and the study *"In utero* exposure and breast cancer: a study in opposite sexed twins" (Study 13). However these studies seemed to relates primarily to oestradiol. *See* Reply of Dr. Boobis to questions of the Panel, Annex D, paras. 493 and 491.

7.690 While the European Communities commented negatively on other considerations by Dr. Boobis, it does not seem to make any specific comment on the remarks of Dr. Boobis on study 11.

7.691 Dr. Sippell mentioned that "the synthetic androgen Trenbolone and the gestagen Melengestrol bind with high affinity to the human androgen and progesterone receptors, respectively (Bauer et al., 2000). Exposure during pregnancy might result in severe transplacental virilisation of a female fetus."[791]

7.692 We note that Dr. Sippell does not indicate at what doses such an effect might occur. It is also not clear whether the last sentence (about exposure during pregnancy) refers to one of the studies identified by the European Communities, or whether it is expressing Dr. Sippell's own opinion. We note, however, that Dr. Boobis said: "There is no basis to think that the effect of hormone growth promoters would be different in any way whatsoever from hormones naturally present in meat, at equivalent internal exposure levels."[792]

7.693 In paragraph 804 of Annex G, Dr. Sippell also states that: "It is, of course, difficult to answer such a question as a clinician, but from the experience we have with the low levels, I mentioned this several times before, with the extremely low levels that have been measured by these new recombinant assays, it is conceivable really that this extra burden of oestradiol poses a risk to very small children and particularly prepubertal boys, and this is in line with the very very high sensitivity of prepubertal children to oestrogens induced for other purposes."[793]

7.694 We consider that, in that paragraph, Dr. Sippell merely argues that it is conceivable that there is a risk, but he is not saying that there is evidence of such a risk. Dr. Sippell also stated: "... I think that as much as children are concerned, we know really by no means enough and the data are really insufficient to tell or to be confident that this additional exposure from hormone-treated meat poses no risk."[794] Dr. Sippell's statements focused on oestradiol.

7.695 At the hearing, Dr. Guttenplan also mentioned: "So the potential genotoxic damage that is done in an adult would overwhelm that that could be done in a child. However, in boys the levels are even lower, and there I think we have to worry about developmental effects, and there has been less said on that – Dr. Sippell has been the major proponent of that – and I still think that these could be investigated epidemiologically or in some type of study. We might, as Dr. Boobis suggested, need a surrogate, perhaps saliva or urine, but I think it is perhaps the most important issue to address is the sensitivity of children. I should also mention hormone-sensitive cancers in post-menopausal women, it could be another concern."[795]

7.696 These two statement express doubts but do not constitute evidence of risks. The Panel notes that science does not stop studying a substance just because there is sufficient evidence to conduct a risk assessment, but continuously re-evaluates substances. Nothing in the above cited passages suggests that the existing evidence was insufficient to complete a risk assessment. In fact, the Panel notes that the European Communities has once again pointed the Panel to evidence that deals only with oestradiol, a hormone for which it claims to have completed a risk assessment. The European Communities has not explained how the interventions from the experts support a conclusion that the scientific evidence was insufficient to conduct a risk assessment with respect to the other five hormones.

[791] Reply of Dr. Sippell to question 41 of the Panel, Annex D, para. 336.
[792] Reply of Dr. Boobis to question 41 of the Panel, Annex D, para. 333.
[793] Annex G, para. 804.
[794] Annex G, para. 1063.
[795] Annex G, para. 1061.

7.697 The European Communities does not provide additional evidence in its comments regarding other hormones than oestradiol.[796]

7.698 Having regard to the opinions of the experts, the Panel is of the view that it has not been established that there is a critical mass of new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient evidence now insufficient in relation to the growth and reproduction effects of the hormones at issue.

(vii) Is relevant scientific evidence insufficient in the case of progesterone

Summary of the main arguments of the parties[797]

7.699 **Canada** argues that, as early as 1981, JECFA evaluated the health effects of residue levels present in human food obtained from animals treated with the naturally occurring hormones, *i.e.* oestradiol-17β, progesterone and testosterone. In the Report of its twenty-fifth meeting, JECFA concluded that residues from the use of these hormones according to good veterinary practices are unlikely to pose a hazard to human health. In 1989, JECFA published the residue monographs for testosterone and progesterone from its thirty-second meeting in June 1987. Each of these reports reviewed several relevant scientific studies on residue levels of these hormones in meat derived from treated animals.

7.700 Canada recalls that, in February 1999, JECFA conducted its most recent comprehensive evaluation of these three naturally occurring hormones. In the Report of its thirty-second meeting, JECFA recommended ADI levels for all three of these substances. JECFA's most recent residue and toxicological monographs for testosterone, progesterone and oestradiol-17β, published in 2000, reference the large number of studies relied on by JECFA to recommend ADIs for these hormones.[798] Canada also notes that hormones such as progesterone and testosterone are endogenously produced chemicals and thus it is unlikely that their transformation products would be of concern.[799]

7.701 Canada concludes that it is evident, based on the scientific data contained in these JECFA reports and the recommended ADIs for these substances, that JECFA does not consider that residues of these hormones have an adverse effect on human health, provided they are used in accordance with good veterinary practices. Canada concludes that, faced with this conclusion from JECFA, the European Communities cannot substantiate its assertion that there is insufficient scientific information to perform an adequate risk assessment in respect of these five hormones.[800]

7.702 The **European Communities** argues that the body of evidence has developed since the *EC – Hormones* case and, while still not providing enough knowledge to carry out a complete and definitive risk assessment, supports the conclusion that precautionary measures are required in order to achieve its chosen level of protection.

7.703 The European Communities, quoting the 1999 Opinion, identifies the following insufficiencies in the evidence:[801]

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[796] EC's comments on replies from experts, question 41, Annex F-1, p. 29.

[797] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[798] Canada's first written submission, paras. 116-124.

[799] Canada's second written submission, para. 134.

[800] Canada's first written submission, paras. 116-124.

[801] EC's second written submission, para. 150.

(a) little knowledge about the specific enzymes in cattle that metabolize progesterone;

(b) considerable uncertainty associated with the validity of daily production rate data used by the US Food and Drug Administration;

(c) no information available on mutagenicity and genotoxicity;

(d) no information available on DNA adducts and DNA damage;

(e) inadequate evidence for carcinogenicity in humans;

(f) regarding effects of progesterone on growth and reproduction, alterations of spermatogenesis can be induced by progesterone treatments, but no assessment of the dose-response relationship is available;

(g) regarding effects on the immune system, there are data indicating that progesterone can cause immuno depression, but they are insufficient to make a realistic assessment of the dose-response relationship.

7.704 In response to Canada's reference to the 1999 JECFA assessment, the European Communities notes that the 1999 Opinion took JECFA's assessment into account, expressing concern regarding the determination of the ADI since neither the actual data nor a reference to a peer-reviewed publication were provided, and since the dose-response was limited to two doses and the ADI was estimated from just a single dose rather than a curve derived from all the data available.[802]

7.705 In addition, the European Communities indicates that the Opinions, in particular the 2002 Opinion, have taken the 1999 CVMP assessment into account. The European Communities argues that the CVMP opinion was not used as the only basis of the EC measure for progesterone as a growth promoter because new scientific evidence had appeared since and the SCVPH assessment had identified risks that were incompatible with the level of health protection applied by the European Communities to these hormones when used for animal growth promotion purposes. Secondly, the European Communities argues that the CVMP conclusion applies only when progesterone is used in veterinary *medicinal* products authorized in accordance with relevant EC legislation, which would exclude over the counter products freely available to laypeople.[803]

Reasoning of the Panel

7.706 In light of the arguments of the parties, and having regard to the 1999 and 2002 Opinions[804] and to the fact that some of the insufficiencies identified by the European Communities have been addressed in the common section above or were simply not discussed by the European Communities in its submissions, the Panel will limit its analysis to determining whether relevant scientific evidence is insufficient concerning progesterone with regard to evidence of carcinogenicity in humans.

[802] EC's second written submission, para. 155; EC's replies to Panel questions after the first substantive meeting, question 22, para.126, Annex B-1.

[803] EC's second written submission, para. 89; EC's replies to Panel questions after the first substantive meeting, question 23, paras. 130-133, Annex B-1.

[804] The 2000 Opinion did not identify essentially new toxicological information concerning progesterone and testosterone in the data presented in the toxicological evaluation of the natural hormones oestradiol-17β, progesterone and testosterone in animal production by JECFA (2000 Opinion, section 2.2, p. 4).

7.707 We note that the European Communities, referring to the 1999 Opinion, argues that there is no information available on the mutagenicity and genotoxicity of progesterone.[805]

7.708 We recall, however, that with respect to genotoxicity, the 2002 Opinion concludes that "[t]here is no evidence that progesterone or testosterone have genotoxic potential."[806]

7.709 Regarding this aspect, we note that Dr. Boisseau quoted the report of JECFA in its thirty-second session (1999), where it concludes that "[a]lthough equivocal results have been reported for the induction of single-strand DNA breaks and DNA adducts have been seen in vivo and in vitro in some studies, progesterone was not mutagenic … progesterone has no genotoxic potential ". Dr. Boisseau also quotes JECFA's conclusion that "these effects on tumour production occurred only with doses of progesterone causing obvious hormonal effects … the effect of progesterone on tumour production was directly related to its hormonal activity".[807]

7.710 Dr. Boobis concurred with the above by saying that:

> "there is no evidence that the hormones testosterone or progesterone have genotoxic potential. ... Micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. In no case did any of the compounds produce a mutagenic response. These data are insufficient to support the conclusion that these hormones have genotoxic potential in vivo. Thus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo."[808]

7.711 Dr. Guttenplan added that "there is no conclusive evidence presented by the European Communities that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential. There is some evidence that certain of the hormones have genotoxic potential, but generally the potential is weak. ... progesterone [is] negative in genotoxic assays. ... Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice."[809]

7.712 The European Communities considers that JECFA was more prudent than the experts when rejecting the genotoxicity of progesterone in 1999. The European Communities further argues that the 1999, 2000 and 2002 risk assessments by the SCVPH provide enough evidence to demonstrate that genotoxicity from these hormones is possible.[810]

7.713 We note that, on the one hand, the SCVPH in its 2002 Opinion concluded "[t]here is no evidence that progesterone or testosterone have genotoxic potential". We note, on the other hand, that the European Communities did not point to any study subsequent to the 2002 Opinion which would contradict this conclusion.

7.714 Regarding evidence of carcinogenicity in humans, we note that IARC has evaluated progestins as *possibly carcinogenic to humans* (Group 2B)[811] based on sufficient evidence of

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[805] EC's second written submission quoting 1999 Opinion, paras. 150-152.
[806] 2000 Opinion, section 4.3, p. 15.
[807] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 157.
[808] Reply of Dr. Boobis to question 21 of the Panel, Annex D, para. 198.
[809] Reply of Dr. Guttenplan to question 21 of the Panel, Annex D, para. 200.
[810] EC's comments to experts' replies to Panel question 21, Annex F-1, p. 18.
[811] In its reply to question 24 of the Panel, Annex E-3, p. 128, IARC mentioned that it uses the following groupings to characterize potential carcinogenic agents:

carcinogenicity in experimental animals.[812] We note, however, that IARC's evaluation relates to the carcinogenicity of hormones in general, not to the carcinogenicity due to exposure to hormone residues in meat and meat products as a result of the cattle being treated with growth promoting hormones.

7.715 Dr. Boisseau mentioned that "[i]n its 1999 report, SCVPH concluded, about the carcinogenicity of progesterone, that 'At present, the data are insufficient to make any quantitative estimate of the risk arising from the exposure to residues in meat.' Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of progesterone are related to a mechanism other than hormonal activity."[813]

7.716 On the basis of the arguments of the parties and of the experts' opinions, we conclude that there is no new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient evidence, now insufficient. We therefore conclude that the elements before us do not support the conclusion that the relevant scientific evidence has become insufficient, within the meaning of Article 5.7 of the *SPS Agreement*, regarding the genotoxicity, mutagenicity and carcinogenicity of progesterone.

Conclusion

7.717 Having regard to our specific conclusions above, we recall that the Appellate Body clarified in *Japan – Apples* that relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1. In this respect, we note that, at our request, the experts also expressed their views on the more general question whether the scientific evidence available at the time of the adoption of Directive 2003/74/EC and subsequently allowed the conduct of a risk assessment, in relation to meat from cattle treated, *inter alia*, with progesterone. Dr. Boobis replied that:

> "[T]here was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue."

"*Carcinogenic to humans* (Group 1). This category is used when there is *sufficient evidence of carcinogenicity* in humans.

Probably carcinogenic to humans (Group 2A). This category is generally used when there is *limited evidence* in humans and *sufficient evidence* in experimental animals.

Possibly carcinogenic to humans (Group 2B). This category is generally used when there is *limited evidence* in humans or *sufficient evidence* in experimental animals, but not both.

Not classifiable as to its carcinogenicity to humans (Group 3). This category is generally used when there is *inadequate evidence* in humans and *inadequate* or *limited evidence* in experimental animals. Agents that do not fall into any other group are also placed in this category.

Probably not carcinogenic to humans (Group 4). This category is generally used when there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals.

Mechanistic and other relevant data also contribute to the grouping. Further details can be found in the Preamble to the *IARC Monographs* (http://monographs.iarc.fr)."

[812] IARC reply to question 25 of the Panel, Annex E-3, p. 129.
[813] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 158.

7.718 We also note Dr. Guttenplan's comment that:

> "Progesterone, testosterone have been extensively investigated and the assessment seems sound and is based on the no effect level and a safety factor. (JECFA meeting 52, report-WHA TRS 893)."

7.719 These general remarks support our conclusions on the specific elements discussed above. We therefore conclude that it is not established that the relevant scientific evidence is insufficient with respect to progesterone, within the meaning of Article 5.7 of the *SPS Agreement*.

(viii) Is relevant scientific evidence insufficient in the case of testosterone?

Summary of the main arguments of the parties[814]

7.720 **Canada** argues that, as early as 1981, JECFA evaluated the health effects of residue levels present in human food obtained from animals treated with the naturally occurring hormones, *i.e.* oestradiol-17β, progesterone and testosterone. In the Report of its twenty-fifth meeting, JECFA concluded that residues from the use of these hormones according to good veterinary practices are unlikely to pose a hazard to human health. In 1989, JECFA published the residue monographs for testosterone and progesterone from its thirty-second meeting in June 1987. Each of these reports reviewed several relevant scientific studies on residue levels of these hormones in meat derived from treated animals.

7.721 Canada recalls that, in February 1999, JECFA conducted its most recent comprehensive evaluation of these three naturally occurring hormones. In the Report of its thirty-second meeting, JECFA recommended ADI levels for all three of these substances. JECFA's most recent residue and toxicological monographs for testosterone, progesterone and oestradiol-17β, published in 2000, reference the large number of studies relied on by JECFA to recommend ADIs for these hormones.[815]

7.722 Canada further notes that JECFA has found that "testosterone is generally considered to be inactive when given by the oral route owing to gastrointestinal and/or hepatic inactivation." Testosterone's low bioavailability dramatically reduces the amount of testosterone which would be available for conversion to estradiol. It should also be noted that hormones such as progesterone and testosterone are endogenously produced chemicals and thus it is unlikely that their transformation products would be of concern.[816]

7.723 Canada concludes that it is evident, based on the scientific data contained in these JECFA reports and the recommended ADIs for these substances, that JECFA does not consider that residues of these hormones have an adverse effect on human health, provided they are used in accordance with good veterinary practices. Canada concludes that, faced with this conclusion from JECFA, the European Communities cannot substantiate its assertion that there is insufficient scientific information to perform an adequate risk assessment in respect of these five hormones.[817]

7.724 The **European Communities**, quoting the 1999 Opinion, identifies the following insufficiencies in the evidence regarding testosterone:[818]

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[814] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[815] Canada's first written submission, paras. 116-124.

[816] Canada's second written submission, para. 134.

[817] Canada's first written submission, paras. 116-124.

[818] EC's second written submission, paras. 153-155.

(a) the mechanism of androgen activity is only partially understood, including the role of androgen receptors in ovarian tumorigenesis;

(b) little information is available about the specific metabolic routes and elimination rates for testosterone in cattle;

(c) there is uncertainty regarding daily production rate data;

(d) genotoxicity of testosterone has not been demonstrated with the limited testing done to date;

(e) no information is available on DNA damage induced by testosterone or its metabolites;

(f) data on carcinogenicity in humans are limited;[819]

(g) no dose-response estimate can be given for effects on growth and reproduction;

(h) there is limited experimental data on the effects of testosterone on the immune system and none on dose-response aspects.

7.725 In response to Canada's reference to the 1999 JECFA assessment, the European Communities notes that the 1999 Opinion questions the quality of the study that provided the data for JECFA's determination of the ADI. According to the European Communities, neither the actual data nor reference to a peer-reviewed publication were provided, the dose-response was limited to two doses and the ADI was estimated from just a single dose where no effect was observed rather than a curve derived from all the data available.[820]

Reasoning of the Panel

7.726 In light of the arguments of the parties, and having regard to the 1999 and 2002 Opinions[821] and to the fact that some of the insufficiencies identified by the European Communities have been addressed in the common section above, or were simply not discussed by the European Communities in its submissions, the Panel does not deem it necessary to address the mechanism of androgen activity, the metabolic routes and elimination rates for testosterone in cattle or the daily production rate data since these issues have either not been discussed specifically by the parties, or were addressed above.

7.727 We also note that the 1999 Opinion found that genotoxicity of testosterone has not been demonstrated with the limited testing done to date.[822] The 2002 Opinion adds that "[t]here is no evidence that progesterone or testosterone have genotoxic potential."[823]

[819] In its conclusion on carcinogenicity, the SCVPH notes that evidence about the role of endogenous testosterone in the occurrence of prostate cancer is weak, that there is limited data on genotoxicity but that testosterone might be aromatized to oestradiol, which had been found to be genotoxic, and that no conclusive quantitative estimate of the risk arising from the excess intake with meat and meat products from treated animals can be made.

[820] EC's second written submission, para. 155; EC's replies to Panel questions after the first substantive meeting, question 22, Annex B-1, para. 124.

[821] The 2000 Opinion did not identify essentially new toxicological information concerning progesterone and testosterone in the data presented in the toxicological evaluation of the natural hormones oestradiol-17β, progesterone and testosterone in animal production by JECFA (2000 Opinion, section 2.2, p. 4).

[822] 1999 Opinion, section 4.2.5.

[823] 2000 Opinion, section 4.3, p. 15. This was confirmed by the experts who expressed views on this question. For instance, Dr. Guttenplan mentioned that: "there is no conclusive evidence presented by the EC that

7.728 Likewise, the 1999 Opinion states that no information is available on DNA damage induced by testosterone or its metabolites.[824] This said, it states that "testosterone is ... aromatized to oestradiol, which is metabolized to reactive forms that damage DNA and induce mutation." The 1999 Opinion then refers to its section on oestradiol-17β.

7.729 The 1999 Opinion also reports that "[W]hereas the evidence in favour of carcinogenicity was considered sufficient for testosterone in experimental animals, data in humans are limited."[825] This reference has to be read in conjunction with the following paragraph of the 1999 Opinion, which states that the evidence regarding the role of testosterone in prostate cancer is currently weak. In addition, it seems to relate to endogenous testosterone. The 1999 Opinion adds that no conclusive quantitative estimate of the risk arising from the excess intake with meat and meat products from treated animals can be made.

7.730 These comments do not, in our opinion, meet our test that there be a critical mass of new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence to make relevant, previously sufficient, evidence now insufficient and would lead us to consider that no risk assessment could be performed. We note in this respect that the 1999 Opinion notes that testosterone is "considered as probable carcinogenic to humans (IARC group 2A)".[826] IARC specified that "this category is generally used when there is limited evidence in humans and sufficient evidence in experimental animals."[827] We also note that IARC assessments are made in general terms, not specifically in relation to consumption of meat treated with hormones for growth promotion purposes.

7.731 Regarding carcinogenicity of testosterone, Dr. Boisseau mentioned that IARC confirms the 1999 Opinion to the extent that it has determined that there is *sufficient evidence of carcinogenicity* in experimental animals and advised, "In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard testosterone as if it presented a carcinogenic risk to humans".[828]

7.732 Dr. Boisseau also stated that "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of testosterone are related to a mechanism other than hormonal activity."[829]

7.733 Having regard to the positions taken by the SCVPH in its 1999 and 2002 Opinions and the views expressed by the experts, we do not find it necessary to address any further the questions of the genotoxicity and carcinogencity of testosterone in our attempt at determining whether relevant scientific evidence is insufficient with respect to this hormone, within the meaning of Article 5.7 of the *SPS Agreement*.

Conclusion

7.734 Having regard to our specific conclusions above, we recall that the Appellate Body clarified in *Japan – Apples* that relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1. In this respect, we note that, at our request, the experts also expressed their views on the more general

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the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential." Reply of Dr. Guttenplan to question 21 of the Panel, Annex D, para. 200.

[824] EC's second written submission, para. 153, quoting 1999 Opinion, pp. 45-51.

[825] EC's second written submission, para. 153, quoting 1999 Opinion, pp. 45-51.

[826] 1999 Opinion, section 4.2.7.

[827] See IARC reply to question 24 of the Panel, Annex E-3, p. 128.

[828] IARC reply to question 25 of the Panel, Annex E-3, p. 129.

[829] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 160.

question whether the scientific evidence available at the time of the adoption of Directive 2003/74/EC and subsequently allowed the conduct of a risk assessment, in relation to meat from cattle treated, *inter alia*, with testosterone. Dr. Boobis replied that:

> "[T]here was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue."

7.735 We also note Dr. Guttenplan's comment that:

> "Progesterone, testosterone have been extensively investigated and the assessment seems sound and is based on the no effect level and a safety factor. (JECFA meeting 52, report-WHA TRS 893)."

7.736 These general remarks support our conclusions on the specific elements discussed above. We therefore conclude that it is not established that the relevant scientific evidence is insufficient with respect to testosterone, within the meaning of Article 5.7 of the *SPS Agreement*.

(ix) Is relevant scientific evidence insufficient in the case of trenbolone acetate?

Summary of the main arguments of the parties[830]

7.737 **Canada** argues that trenbolone acetate and zeranol were first considered by JECFA in 1982 and again in 1983. In 1987, JECFA prepared residue and toxicity monographs for trenbolone acetate and zeranol. In the Report of its thirty-second meeting JECFA recommended an ADI for zeranol. Further residue and toxicity monographs were prepared by JECFA for its thirty-fourth meeting in 1989. Based on JECFA's analysis of the toxicological data produced for this meeting, JECFA recommended an ADI for trenbolone acetate.[831]

7.738 Canada adds that JECFA reviewed genotoxicity and mutagenicity data for trenbolone acetate and its metabolites TBOH alpha and TBOH beta at its thirty-second and thirty-fourth meetings and concluded that it was unlikely that they were genotoxic.[832]

7.739 Canada considers that, based on the scientific data contained in these JECFA reports and the recommended ADIs for these substances, JECFA does not consider that residues of these hormones have an adverse effect on human health, provided they are used in accordance with good veterinary practices. Canada concludes that, faced with this conclusion from JECFA, the European Communities cannot substantiate its assertion that there is insufficient scientific information to perform an adequate risk assessment in respect of these five hormones.[833]

7.740 The **European Communities**, quoting the 1999 Opinion, identifies the following insufficiencies in the scientific evidence:[834]

(a) the need to further investigate the metabolic fate and chemical nature of covalently bound residues of trenbolone acetate;[835]

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[830] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[831] Canada's first written submission, paras. 116-124.

[832] Canada's second written submission, para. 135.

[833] Canada's first written submission, paras. 116-124.

[834] EC's second written submission, paras. 156-157.

[835] EC's second written submission, para. 156, quoting 1999 Opinion, pp. 55-60.

(b) in humans, no data are currently available to assess the carcinogenicity of trenbolone acetate;[836]

(c) regarding effects on reproduction, the available data do not allow a realistic assessment of a dose-response relationship;

(d) investigations of the effects of trenbolone acetate on the immune system are very limited.

7.741 The European Communities adds that the SCVPH concluded that the information is insufficient to assess the possible impacts of low levels of trenbolone acetate in meat on consumers.

7.742 The European Communities indicates that, in its 2002 Opinion, the SCVPH found these conclusions to be compounded by data obtained in certain of the 17 studies and more recent research, none of which was considered by the 1988 JECFA report. The European Communities argues that the only assessment on trenbolone acetate publicly available is that of JECFA, and that the SCVPH took this assessment into account, but disagreed with a number of its basic findings on the basis of more recent scientific research.[837]

Reasoning of the Panel

7.743 In light of the arguments of the parties and of the fact that some of the insufficiencies identified by the European Communities have been addressed in the common section above, or were simply not discussed by the European Communities in its submissions, the Panel will limit its analysis to determining whether relevant scientific evidence is insufficient concerning trenbolone acetate with regard to the following aspects:

(a) metabolism of trenbolone acetate;

(b) inadequate evidence of carcinogenicity in humans.

Metabolism of trenbolone acetate

7.744 The European Communities refers to the 2002 Opinion which states that "experiments with zeranol and trenbolone acetate suggested a more complex oxidative metabolism than previously assumed. These data need further clarification as they might influence a risk assessment related to tissue residues of these compounds."[838]

7.745 We note that Dr. Boobis discussed study 4 of the 17 studies:[839]

> "The metabolism of zeranol and trenbolone had been further investigated (study 4). These data do not appear to have been published in the peer reviewed literature to date.

[836] In its conclusion on carcinogenicity, the SCVPH notes that in consideration of the lack of *in vitro* short-term assays on mutagenicity and genotoxicity of certain TBOH metabolites and in consideration of the equivocal results of cell transformation assays and the *in vivo* studies, the available information is insufficient to complete a quantitative risk assessment. 1999 Opinion, section 4.4.7, p. 59.

[837] EC's second written submission, paras. 156-157; EC's replies to Panel questions after the first substantive meeting, question 22, Annex B-1, para. 126.

[838] EC's second written submission, para. 156, quoting 1999 Opinion at pp. 55-60.

[839] 2002 Opinion, section 7, p. 21.

> The data on trenbolone show that the alpha enantiomer in liver slices from bovine is extensively conjugated and hence inactivated. There is some conversion of the alpha to the active beta isomer by human liver microsomes, but the kinetics of the reaction and the extent of conjugation have not been determined. No data were presented on levels of the alpha enantiomer in meat from treated cattle. However, these data do not affect the risk assessment of trenbolone acetate. This is because a) the toxicological studies were conducted in animals that would have been exposed to the metabolites of concern, b) JECFA considered residues of both the alpha and the beta enantiomers in recommending MRLs for trenbolone acetate."[840]

7.746 No other expert expressed views on the subject.

7.747 The Panel is cognizant that the European Communities argues that Dr. Boobis' comments on a number of the studies generated by the European Communities are flawed and has given examples of those alleged flaws.[841] However, it does not expressly address Dr. Boobis' comments on the study discussed above. As a result, the Panel sees no reason not to take the comments of Dr. Boobis fully into account in its assessment of the sufficiency of existing relevant scientific evidence.

Inadequate evidence of carcinogenicity in humans

7.748 The European Communities refers to the 1999 Opinion which recalls that trenbolone acetate is a synthetic androgen and that both the parent compound and its metabolite have been extensively tested for their mutagenic/genotoxic potential. The 1999 Opinion notes that it might be concluded that the genotoxic effects of trenbolone acetate are not related to their hormonal activity. It notes that "[f]ormation of DNA adducts has been observed in rat hepatocytes ... (Metzler, 1999)." On carcinogenicity, the 1999 Opinion mentions *inter alia* that a two-year carcinogenesis[842] bioassay in rats and mice did not provide definitive results. In humans, no data are currently available to assess the carcinogenicity of trenbolone acetate. The 1999 Opinion concludes that the available information is insufficient to complete a quantitative risk assessment.[843]

7.749 Regarding this aspect, Dr. Boisseau mentioned the following:

> "In its thirty second session held in 1987, JECFA concluded from carcinogenic studies in animals that "the liver hyperplasia and tumours in mice … and the slight increase in the incidence of islet-cell of the pancreas of rats arose as a consequence of the hormonal activity of trenbolone". In its thirty fourth session held in 1989, JECFA, having reviewed a comprehensive battery of short term tests, concluded that 'it was unlikely that trenbolone acetate was genotoxic' and decided to confirm its previous

[840] Reply of Dr. Boobis to question 62 of the Panel, Annex D, paras. 479-480.
[841] EC's comments on the replies of the experts, Annex F-1, p. 40.
[842] *Mechanism (or mode of action) of carcinogenesis:* a mode of action is series of key events which are necessary to lead to the formation of a tumour. These key events comprise the biological changes induced by the chemical and subsequent events which then lead to the development of cancer. A mechanism refers to the molecular events that are responsible for those changes. A hormonal mechanism means that it is the endocrine or hormonal effect of a compound that leads to growth or proliferation of certain cells that are responsive to the hormone, resulting in the development of a tumour. A genotoxic mechanism means that there is a mechanism independent of the hormonal action resulting in direct damage to the DNA that leads to a tumour. There are situations where elements of more than one mechanism could apply (Transcript of the Panel meeting with the experts, (Dr. Boobis, Dr. Cogliano and Dr. Guttenplan), Annex G, paras. 103-109).
[843] 1999 Opinion, pp. 57-59.

> conclusion to base the evaluation of trenbolone acetate and its metabolites on their no-hormonal-effect."[844]

7.750 The 2002 Opinion refers to the results of study 2 of the 17 studies with respect to mutagenicity and genotoxicity (Metzler and Pfeiffer, 2001).[845]

7.751 Three experts expressed their views in relation to the subject of this study. Dr. Boobis mentions the following:

> "There is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic. They were negative in a range of tests for genotoxicity. They were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. Trenbolone also produced a low level of DNA adducts measured by 32P-post-labelling *(Metzler and Pfeiffer, 2001)*.[846] As indicated above, micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. In no case did any of the compounds produce a mutagenic response. These data are insufficient to support the conclusion that these hormones have genotoxic potential in vivo. Thus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo."[847]

7.752 Dr. Boobis added that:

> "Study 4 reports recent observations on the genotoxicity and mutagenicity of zeranol and trenbolone. Both compounds were negative for tests of mutagenicity, i.e. induction of *lac*I mutations in *E coli* and induction of *hprt* mutations inV79 cells. Zeranol did not produce DNA adducts in rat hepatocytes whilst a low level of DNA adducts was observed with trenbolone. Both were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. As indicated above ..., micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. These data are insufficient, given the number of well conducted studies in which the compounds were negative, to alter the conclusion that neither zeranol nor trenbolone acetate has genotoxic potential in vivo. Indeed, the *SVCPH (2002)* concluded that "both compounds exhibited only very weak effects" in those in vitro tests in which positive effects were observed."[848]

7.753 Dr. Guttenplan confirmed the conclusions of the two other experts:

> "[t]here is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential.

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[844] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 163.
[845] 2002 Opinion, section 4.4.3.
[846] Dr. Boobis cited to Metzler M and Pfeiffer E (2001). Genotoxic potential of xenobiotic growth promoters and their metabolites. APMIS, **109**:89-95
[847] Reply of Dr. Boobis to question 21 of the Panel, Annex D, para. 198.
[848] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 483.

> There is some evidence that certain of the hormones have genotoxic potential, but generally the potential is weak. ... Trenbolone is either negative or marginally active in *in vitro* genotoxic assays. ... Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice. My reply for the hormones would not have been different in September 2003 (SCVPH 2002 Opinion)."[849]

7.754 The European Communities argues essentially that the 1999, 2000 and 2002 Opinions provide enough evidence to demonstrate that genotoxicity and other adverse effects from these hormones are possible and that there are a number of uncertainties surrounding their mechanism of action to warrant further investigations. The European Communities refers to Dr. Guttenplan's statement.[850]

7.755 We do not read the statement above as the European Communities does. Rather we understand Dr. Guttenplan to say that the genotoxic potential of trenbolone acetate is weak.

7.756 Regarding carcinogenicity, we first note that trenbolone acetate has not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with this growth promotion hormone.[851]

7.757 Dr. Boisseau made the following comments:

> "In its 1999 report, SCVPH concluded, about the carcinogenicity of trenbolone, that 'in consideration of the lack of in vitro short term assays on mutagenicity and genotoxicity of other trenbolone metabolites other than α-trenbolone and in consideration of the equivocal results of the transformation assays and the in vivo studies, the available information is insufficient to complete a quantitative risk assessment'. Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of trenbolone are related to a mechanism other than hormonal activity."[852]

7.758 The European Communities seeks to refute Dr. Boisseau's comments on the basis that he refers only to the JECFA's reports, which are outdated and based on old data, and that he interprets lack of data as lack of adverse effects.

7.759 We recall our test in order to assess whether relevant scientific evidence is insufficient is that there should be new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient evidence, now insufficient. We note that the European Communities points at possibilities which are not confirmed by the experts who expressed their views. We therefore conclude that the elements before us do not support the conclusion that the relevant scientific evidence has become insufficient, within the meaning of Article 5.7 of the *SPS Agreement*, regarding the carcinogenicity of trenbolone acetate.

Conclusion

7.760 Having regard to our specific conclusions above, we recall that the Appellate Body clarified in *Japan – Apples* that relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1. In this respect, we note that, at our request, the experts also expressed their views on the more general

[849] Reply of Dr. Guttenplan to question 21 of the Panel, Annex D, para. 200.
[850] EC's comments on replies to question 21 of the experts, Annex F-1, p. 18.
[851] IARC reply to question 25 of the Panel, Annex E-3, p. 129.
[852] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 164.

question whether the scientific evidence available at the time of the adoption of Directive 2003/74/EC and subsequently allowed the conduct of a risk assessment, in relation to meat from cattle treated, *inter alia*, with trenbolone acetate. Dr. Boobis replied that:

> "[T]here was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue."

7.761 We also note Dr. Guttenplan's comment that:

> "There is more limited evidence available for Trenbolone and Zeranol and most of it is *in vitro* (*SCVPH 2002 Opinion*) or not recent (e.g., JECFA meeting 34th report, 1989 and 32nd report, 1988). However, both appear to be potentially significantly estrogenic. Experimental and analytical methods have improved but it does not appear that accurate ADI's can be established at this point. Studies in experimental animals and studies on levels in beef are still needed. However, from the data available at the time of the Directive, the potential for adverse effects could not be ruled out."[853]

7.762 We note, however, that during our meeting with the experts, Dr. Guttenplan clarified, at the EC request, that "the ability [to make a risk assessment] varies between compounds, but that does not mean that you can't make a risk assessment, it just means that the accuracy of the risk assessment is different."[854] Regarding the establishment of accurate ADIs, Dr. Guttenplan clarified that "accurate means – if it's not accurate, there is just a larger range, but you can still do a risk assessment."[855]

7.763 These general remarks support our conclusions on the specific elements discussed above. We therefore conclude that it is not established that the relevant scientific evidence is insufficient with respect to trenbolone acetate, within the meaning of Article 5.7 of the *SPS Agreement*.

(x) Is relevant scientific evidence insufficient in the case of zeranol

Summary of the main arguments of the parties[856]

7.764 **Canada** recalls that trenbolone acetate and zeranol were first considered by JECFA in 1982 and again in 1983. In 1987, JECFA prepared residue and toxicity monographs for trenbolone acetate and zeranol. In the Report of its thirty-second meeting JECFA recommended an ADI for zeranol. Further residue and toxicity monographs were prepared by JECFA for its thirty-fourth meeting in 1989. Based on JECFA's analysis of the toxicological data produced for this meeting, JECFA recommended an ADI for trenbolone acetate.[857]

7.765 Canada adds that JECFA has found that zeranol and its metabolites zearalanone and taleranol not to be mutagenic in a number of tests in bacterial and mammalian systems.[858]

7.766 In Canada's opinion, it is evident, based on the scientific data contained in these JECFA reports and the recommended ADIs for these substances, that JECFA does not consider that residues

[853] Reply of Dr. Guttenplan to question 61 of the Panel, Annex D, para. 457.
[854] Transcript of the Panel meeting with the experts, Annex G, para. 983.
[855] Transcript of the Panel meeting with the experts, Annex G, para. 985.
[856] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.
[857] Canada's first written submission, paras. 116-124.
[858] Canada's second written submission, para. 135.

of these hormones have an adverse effect on human health, provided they are used in accordance with good veterinary practices. Canada concludes that, faced with this conclusion from JECFA, the European Communities cannot substantiate its assertion that there is insufficient scientific information to perform an adequate risk assessment in respect of these five hormones.[859]

7.767 The **European Communities**, quoting the 1999 Opinion, identifies the following insufficiencies in the evidence:[860]

(a) there are only few tests with equivocal results on the genotoxic properties of zeranol, which are insufficient for an evaluation of its mutagenic/genotoxic properties;

(b) no data are available on cancer risk for humans linked to meat with zeranol residues;[861]

(c) no dose-response relationship for effects of zeranol on growth and reproduction can be made;

(d) no relevant data on effects on the immune system were found.

7.768 The European Communities notes that, in conclusion, the 1999 Opinion finds that the available data do not allow a quantitative estimate of the risk arising from exposure to zeranol residues, and that further data are needed on the nature of the metabolites formed in bovines. The European Communities indicates that in its 2002 Opinion, the SCVPH found these conclusions to be compounded by data obtained in certain of the 17 studies and more recent research.[862]

7.769 The European Communities cites a study by US scientists according to which meat and serum from zeranol-implanted cattle possess "heat-stable mitogenicity for cultured breast cells, and that both normal and cancerous human breast cells exhibit estrogenic responses to zeranol".[863] These scientists then point to potential tumorigenic effects for oestrogen, including direct genotoxic effects of oestrogen metabolites. They point out that the mechanisms responsible for oestrogen stimulated carcinogenesis remain undefined. The European Communities argues that these studies clearly invalidate the findings of the 1988 JECFA opinion.[864]

7.770 The European Communities also argues that the only assessment on zeranol publicly available is that performed by JECFA in 1988. The European Communities indicates that the SCVPH took this assessment into account, but disagreed with a number of its basic findings on the basis of more recent scientific research, some of which was generated by the 17 studies[865] (studies Nos. 2, 4 and 10) and more recent research.

[859] Canada's first written submission, paras. 116-124.
[860] EC's second written submission, paras. 158-160.
[861] In its conclusion on carcinogenicity, the SCVPH states that considering the limited data on mutagenicity/genotoxicity and the clear evidence for an induction of liver adenomas and carcinomas in hamsters, no assessment of the possible carcinogenicity of zeranol can be made. See 1999 Opinion, section 4.5.7, p. 65.
[862] EC's second written submission, paras. 158-160.
[863] EC's second written submission, paras. 139-140, citing a study by Suling Liu and Young C. Lin, Exhibit EC-8.
[864] EC's second written submission, para. 160.
[865] EC's second written submission, paras. 158-159; EC's replies to Panel questions after the first substantive meeting, question 22, Annex B-1, para. 126.

Reasoning of the Panel

7.771 In light of the arguments of the parties and of the fact that some of the insufficiencies identified by the European Communities have been addressed in the common section above, or were simply not discussed by the European Communities in its submissions, the Panel will limit its analysis to determining whether relevant scientific evidence is insufficient concerning zeranol with regard to the alleged inadequate evidence of carcinogenicity in humans, such as lack of information available on mutagenicity and genotoxicity and lack of information on DNA adducts and DNA damages.

7.772 The 1999 Opinion referred to by the European Communities states that the mutagenicity and genotoxicity of zeranol was investigated only in a few tests which gave equivocal results insufficient for an evaluation of the mutagenic/genotoxic properties of zeranol. As far as carcinogenicity is concerned, the 1999 Opinion concludes that there is clear evidence for the induction of liver adenomas and carcinomas in one animal species, but no assessment of the possible carcinogenicity of zeranol can be made.[866]

7.773 Five experts provided views on this matter. Dr. Cogliano limited his comments to the study by Norat et al. (2005)[867], one of the three recently published studies on which the Panel sought the views of the experts, which addresses the association between consumption of red meat and colorectal cancer. The comments by Dr. Cogliano are not specific with respect to the question of the potential carcinogenicity of zeranol.

7.774 Dr. Boisseau expressed the following opinion:

> "In its thirty second session held in 1987, JECFA concluded that zeranol and its metabolites, zearalanone and taleranol, were not mutagenic in a number of tests in bacterial and mammalian systems even if it has noted that zeranol gives a positive result in the Rec-assay and taleranol gives a positive result in the test with Chinese hamster ovary cells in the absence of activation but a negative result with activation. After having reviewed the carcinogenicity studies in animals, JECFA concluded that 'the tumorigenic effect of zeranol was associated with its oestrogenic properties'."[868]

7.775 The 2002 Opinion refers to a comparative study (study 4 of the 17 studies) designed to determine the potential of zeranol, trenbolone and melengestrol acetate to cause genetic damages in various *in vitro* systems. The 2002 Opinion states that "[i]n this study zeranol did not induce genotoxicity or mutagenicity."[869]

7.776 Dr. Sippell mentioned that "[S]ynthetic hormone growth promoters such as Zeranol and its metabolites have been shown to be as potent as [estradiol] and diethylstilbestrol (DES) in increasing the expression of estrogen-related genes in human breast cancer cells (*Leffers et al 2001* – study 17)."[870] However, Dr. Boobis specified that:

> "The study referred to (study 17), reported in *Leffers et al (2001)*, showed that a number of oestogenic compounds affected the expression of several genes in the ER positive breast cancer cell line, MCF7. The responsiveness of this cell line to oestrogens is well established. It was of interest that all of the changes reported by *Leffers et al (2001)* were blocked by the selective ERantagonist ICI82.780. The

[866] 1999 Opinion, sections 4.5.5 to 4.5.7.
[867] Exhibit EC-71.
[868] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 165.
[869] 2002 Opinion, section 4.4.3, p. 16.
[870] Reply of Dr. Sippell to question 41 of the Panel, Annex D, para. 336.

relevance of effects observed in a cultured cell line to the situation *in vivo*, where kinetic and metabolic factors will influence the magnitude of the response is not known, nor is the significance of changes in gene expression to the toxicity of the hormones known. Many of the changes will reflect the proliferative response to an oestrogenic stimulus. However, in general toxicogenomic data, in the absence on any information on the functional consequences, is not considered a sound basis for use in risk assessment *(IPCS, 2003)*."[871]

7.777 Dr. Boobis added that:

"There is no evidence that the hormones testosterone or progesterone have genotoxic potential. There is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic. They were negative in a range of tests for genotoxicity. They were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. Trenbolone also produced a low level of DNA adducts measured by 32P-post-labelling *(Metzler and Pfeiffer, 2001)*.[872] As indicated above, micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. In no case did any of the compounds produce a mutagenic response. These data are insufficient to support the conclusion that these hormones have genotoxic potential in vivo. Thus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo."

7.778 Dr. Boobis, commenting on study 4, added the following:

"Study 4 reports recent observations on the genotoxicity and mutagenicity of zeranol and trenbolone. Both compounds were negative for tests of mutagenicity, i.e. induction of *lac*I mutations in *E coli* and induction of *hprt* mutations inV79 cells. Zeranol did not produce DNA adducts in rat hepatocytes whilst a low level of DNA adducts was observed with trenbolone. Both were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. As indicated above ..., micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. These data are insufficient, given the number of well conducted studies in which the compounds were negative, to alter the conclusion that neither zeranol nor trenbolone acetate has

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[871] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 475. Dr. Boobis cites to:

IPCS (2003). Toxicogenomics and the Risk Assessment of Chemicals for the Protection of Human Health
(http://www.who.int/entity/ipcs/methods/en/toxicogenomicssummaryreport.pdf)

Leffers H, Naesby M, Vendelbo B, Skakkebaek NE and Jorgensen M (2001). Oestrogenic potencies of Zeranol, oestradiol, diethylstilboestrol, Bisphenol-A and genistein: implications for exposure assessment of potential endocrine disrupters. Hum Reprod, **16**:1037-1045.

[872] Dr. Boobis cited to Metzler M and Pfeiffer E (2001). Genotoxic potential of xenobiotic growth promoters and their metabolites. APMIS, **109**:89-95. See Reply of Dr. Boobis to question 21 of the Panel, Annex D, para. 198.

genotoxic potential in vivo. Indeed, the *SVCPH (2002)* concluded that "both compounds exhibited only very weak effects" in those in vitro tests in which positive effects were observed."[873]

7.779 Dr. Guttenplan commented in more general terms that:

"There is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential. There is some evidence that certain of the hormones have genotoxic potential, but generally the potential is weak. .... Zeranol can induce transformation of breast epithelial cells in culture with efficiency similar to that of estradiol, but the mechanism is not known, and it is negative or marginally active in other assays. ... Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice. My reply for the hormones would not have been different in September 2003 (*SCVPH 2002 Opinion*)."[874]

7.780 Regarding carcinogenicity of zeranol, Dr. Boisseau mentioned that:

"In its 1999 report, SCVPH concluded, about the carcinogenicity of zeranol, that "in consideration of the lack of data on mutagenicity/genotoxicity and the clear evidence for an induction of liver adenomas and carcinomas in one animal species, no assessment of the possible carcinogenicity of zeranol can be made". Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of zeranol are related to a mechanism other than hormonal activity."[875]

7.781 Referring to the study by Liu S and Lin YC (2002)[876], Dr. Guttenplan stated that:

"The first of the studies suggests a risk from zeranol. That observation was not previously reported. However, the results were obtained in cultured cells and the relevance to human exposure to hormone-treated cannot be extrapolated from this study because of a myriad of uncertainties in such extrapolation. The study does suggest that additional tests of zeranol should be carried out. There is also some evidence that a metabolite of zeranol (zearalenone) induces oxidative damage in cultured cells. This is a possible genotoxic effect, but again it cannot be extrapolated to meat consumption."[877]

7.782 Zeranol has not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with this growth promotion hormone.[878]

7.783 The European Communities argues that Dr. Guttenplan made a "careful and scientifically sound statement".[879] We note, however, that Dr. Guttenplan concluded that a genotoxic effect cannot be extrapolated to meat consumption, because of the "myriad of uncertainties" that such extrapolation would entail.

[873] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 483.
[874] Reply of Dr. Guttenplan to question 21 of the Panel, Annex D, para. 200.
[875] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 166.
[876] Liu S and Lin YC (2004). Transformation of MCF-10A human breast epithelial cells by zeranol and oestradiol-17beta. Breast J, 10:514-521, Exhibit EC-62.
[877] Reply of Dr. Guttenplan to question 25 of the Panel, Annex D, para. 234.
[878] IARC reply to question 25 of the Panel, Annex E-3, p. 129.
[879] EC's comments on reply 25 to the questions of the Panel to the experts, Annex F-1, p. 21.

7.784 On the basis of the arguments of the parties and of the experts' opinions, we conclude that it is not established that relevant scientific evidence is insufficient in relation to the carcinogenicity of zeranol, within the meaning of Article 5.7 of the *SPS Agreement*.

Conclusion

7.785 Having regard to our specific conclusions above, we recall that the Appellate Body clarified in *Japan – Apples* that relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1. In this respect, we note that, at our request, the experts also expressed their views on the more general question whether the scientific evidence available at the time of the adoption of Directive 2003/74/EC and subsequently allowed the conduct of a risk assessment, in relation to meat from cattle treated, *inter alia*, with zeranol. Dr. Boobis replied that:

> "[T]here was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue."

7.786 We also note Dr. Guttenplan's comment that:

> "There is more limited evidence available for Trenbolone and Zeranol and most of it is *in vitro* (*SCVPH 2002 Opinion*) or not recent (e.g., JECFA meeting 34th report, 1989 and 32nd report, 1988). However, both appear to be potentially significantly estrogenic. Experimental and analytical methods have improved but it does not appear that accurate ADI's can be established at this point. Studies in experimental animals and studies on levels in beef are still needed. However, from the data available at the time of the Directive, the potential for adverse effects could not be ruled out."[880]

7.787 We note, however, that during our meeting with the experts, Dr. Guttenplan clarified, at the EC request, that "the ability [to make a risk assessment] varies between compounds, but that does not mean that you can't make a risk assessment, it just means that the accuracy of the risk assessment is different."[881] Regarding the establishment of accurate ADIs, Dr. Guttenplan clarified that "accurate means – if it's not accurate, there is just a larger range, but you can still do a risk assessment."[882]

7.788 These general remarks support our conclusions on the specific elements discussed above. We therefore conclude that it is not established that the relevant scientific evidence is insufficient with respect to zeranol, within the meaning of Article 5.7 of the *SPS Agreement*.

(xi) Is relevant scientific evidence insufficient in the case of melengestrol acetate (MGA)?

Summary of the main arguments of the parties[883]

7.789 **Canada** argues that melengestrol acetate is the most recent hormone to be evaluated by JECFA. This hormone was evaluated by JECFA at its fifty-fourth meeting in 2000. In 2004, JECFA further evaluated its recommendations for melengestrol acetate in the light of the new data contained

[880] Reply of Dr. Guttenplan to question 61 of the Panel, Annex D, para. 457.
[881] Transcript of the Panel meeting with the experts, Annex G, para. 983.
[882] Transcript of the Panel meeting with the experts, Annex G, para. 985.
[883] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

in three residue monographs prepared in advance of its sixty-second meeting. In the Report of this meeting, JECFA recommended an ADI for melengestrol acetate.[884]

7.790 Canada adds that JECFA has noted that melengestrol acetate does not contain a structural alert for mutagenicity and genotoxicity and found that in a series of mutagenicity and genotoxicity tests the results were negative.[885]

7.791 Canada is of the view that, based on the scientific data contained in these JECFA reports and the recommended ADIs for these substances, JECFA does not consider that residues of these hormones have an adverse effect on human health, provided they are used in accordance with good veterinary practices. Canada concludes that, faced with this conclusion from JECFA, the European Communities cannot substantiate its assertion that there is insufficient scientific information to perform an adequate risk assessment in respect of these five hormones.[886]

7.792 The **European Communities**, quoting passages the 1999 Opinion, identified the following insufficiencies in the evidence:[887]

(a) only limited data are available concerning MGA residues in treated cattle;

(b) no information is available on mutagenicity and genotoxicity;

(c) no information is available on DNA adducts and DNA damage;

(d) carcinogenicity studies have been conducted in only one animal species, which is inadequate to assess the carcinogenic potential of melengestrol acetate;[888]

(e) available data on effects of melengestrol acetate on growth and reproduction do not allow an estimate of the dose-response relationship;

(f) data on the effect of melengestrol acetate on the immune system are also very limited.

7.793 The European Communities adds that the SCVPH concluded that the available information is insufficient for a quantitative estimate of the risk to the consumer of meat from treated animals. The European Communities indicates that in its 2002 Opinion, the SCVPH found these conclusions compounded by data obtained in certain of the 17 studies.

7.794 The European Communities recalls the finding of the Appellate Body in *EC – Hormones* that no risk assessment had been performed and notes that Codex has not adopted an international standard on melengestrol acetate, although JECFA assessed melengestrol acetate in 2000 (and in 2004 as regards calculation of the MRL). The European Communities argues that in the absence of a Codex standard, the opinion of JECFA becomes irrelevant. In addition, the European Communities indicates that JECFA failed to take into account the more recent data generated by its 17 studies and the 2002 Opinion.[889]

[884] Canada's first written submission, paras. 116-124.
[885] Canada's second written submission, para. 135.
[886] Canada's first written submission, paras. 116-124.
[887] EC's second written submission, paras. 161-166.
[888] In its conclusion on carcinogenicity, the SCVPH notes that in view of the lack of data on mutagenicity/carcinogenicity and on DNA interaction, and in consideration of carcinogenicity studies conducted only in one animal species, the data are inadequate to assess the carcinogenetic potential of MGA.
[889] EC's second written submission, para.161.

7.795 The European Communities notes that the SCVPH took into account the JECFA assessment and noted that no original data had been presented in the JECFA report and that the majority of references were to reports that had not been published in the peer-reviewed scientific literature.[890]

7.796 The European Communities refers to a draft 2005 report from the UK Committee on Veterinary Practices. According to the European Communities, this report notes that there are important gaps in the evidence base for oestradiol-17β and the other five hormonally-active substances, as acknowledged in the Opinion. The cited passage then states a need for certain information, including a number of issues where more information is needed to improve future risk assessments.[891]

7.797 The European Communities concludes that there is no doubt that the 1999-2002 Opinions constitute the only currently available risk assessment on melengestrol acetate, based on the most recent, peer-reviewed, pertinent information available publicly from the European Communities. The European Communities notes that these Opinions reached the conclusion that the current state of scientific knowledge does not permit a more definitive risk assessment to be carried out.[892]

Reasoning of the Panel

7.798 In light of the arguments of the parties and of the fact that some of the insufficiencies identified by the European Communities have been addressed in the common section above, or were simply not discussed by the European Communities in its submissions, the Panel will limit its analysis to determining whether relevant scientific evidence is insufficient concerning melengestrol acetate with regard to the following aspects:

(a) only limited data are available concerning MGA residues in treated cattle;

(b) inadequate evidence for carcinogenicity in humans, such as no information available on mutagenicity and genotoxicity and no information available on DNA adducts and DNA damage. [893]

7.799 As a preliminary remark, the Panel notes that Codex did not adopt any standard with respect to melengestrol acetate. The Panel recalls, however, that while there is no international standard as such, intensive work has been performed at the international level. JECFA made two assessments of melengestrol acetate in 2000 and 2004 (the second time in order to propose a MRL). It was included in the priority list for recalculation of MRLs and TMDI by the fifteenth session of CCRVDF that met in 2005.[894] The Panel notes in this respect that for melengestrol acetate, the draft MRL is currently at Step 7 of the Codex elaboration procedure.[895] Moreover, the role of JECFA in the international risk assessment process is such that some degree of relevance should be given to that work. The Panel also notes that at no time did the European Communities request that melengestrol acetate be considered by Codex.[896]

[890] EC's second written submission, para.164; EC's replies to Panel questions after the first substantive meeting, question 22, Annex B-1, paras. 126-127.
[891] EC's second written submission, para.165.
[892] EC's second written submission, para.166.
[893] EC's second written submission, para. 162, quoting 1999 Opinion, p. 77.
[894] Dr. Miyagishima, Codex representative, transcript of the Panel meeting with the experts, Annex G, para. 524.
[895] As explained by Dr. Miyagishima, Codex representative. See transcript of the Panel meeting with the experts, Annex G, para.896.
[896] Dr. Miyagishima, transcript of the Panel meeting with the experts, Annex G, para. 524.

Data on residues of melengestrol acetate

7.800 The two main criticisms of the European Communities regarding JECFA' s assessments are that the residue data used by JECFA on MGA are outdated and that JECFA did not take into account the more recent studies commissioned by the European Communities. In the 2002 Opinion, the SCVPH noted that in the JECFA report no original data had been presented and that the majority of references were to reports that had not been published in the peer-reviewed scientific literature.[897]

7.801 We sought the views of the experts on this matter and two of them gave an opinion (Dr. Boisseau, Dr. De Brabander). Both concurred in saying that nearly all the studies used by JECFA dated back to the 1960s and 1970s. However, neither of the two experts stated that these studies were no longer valid.[898]

7.802 The Panel first recalls its position on so-called "old" data in paragraph 7.414 *et seq*. above.

7.803 Second, the Panel notes the opinion of Dr. Boisseau: "It is correct to say that nearly all the studies referred to in the 2000 JECFA report on melengestrol acetate date from the 1960s and 1970s. The comment to be made on this issue is [that] JECFA considered a wide series of toxicological studies in its assessment, used as an end point a non hormonal effect dose by far more conservative than a NOAEL based on tumorigenic effect and adopted a 200 safety factor to derive an ADI from this NOAEL."[899]

7.804 Dr. Boobis also expressed his views on the more recent studies commissioned by the European Communities. With respect to the findings of study 4 referred to by the European Communities regarding residues of melengestrol acetate, Dr. Boobis mentioned the following:

> "In study 4, unpublished preliminary findings on the in vitro metabolism of MGA were reported. This study provided some evidence for the formation of multiple metabolites of MGA by liver from human, rat and bovine. However, these findings do not affect the risk assessment of MGA because a) the toxicological studies were conducted in animals that would have been exposed to all of the metabolites of concern, b) JECFA assumed that all of the residues in meat from animals treated with MGA were as hormonally active as MGA when it proposed MRLs in 2002 *(JECFA, 2002b)*. It was subsequently shown that this was a conservative decision, as not all of the residues were as active as MGA itself *(JECFA, 2006c)."*[900]

7.805 Although the European Communities criticized Dr. Boobis' analysis of some of the 17 studies in its comments on the replies of the experts[901], it did not specifically address Dr. Boobis' comments on study 4.

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[897] 2002 Opinion, p. 16.
[898] Reply of Dr. De Brabander to question 35 of the Panel, Annex D, paras. 304-305.
[899] Reply of Dr. Boisseau to question 35, Annex D, para. 303.
[900] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 484. Dr. Boobis cites to:

– JECFA (2002b). Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper 41/14, Rome, Italy; and

– JECFA (2006c). Residues of some veterinary drugs in animals and foods. FAO, Rome, Italy (in press).

[901] EC's comments on the replies of the experts, Annex F-1, p. 40.

> Inadequate evidence for carcinogenicity in humans, such as no information available on mutagenicity and genotoxicity and no information available on DNA adducts and DNA damage

7.806 We note that the 2002 Opinion mentions that the genotoxicity of melengestrol acetate was investigated (study 4) and that "[t]he results were negative in several experiments using concentrations in either 15-125 uM for HPRT mutations, 20-100 uM for micronuclei induction, and 400uM for LacI mutations."[902]

7.807 This statement seems to confirm JECFA's conclusions, as recalled by Dr. Boisseau:

> "[I]n its fifty fourth session, JECFA concluded from the review of a range of assays in vitro and in vivo that melengestrol acetate is not genotoxic. It also agreed upon the fact that 'no firm conclusion could be drawn about the carcinogenic potential of melengestrol acetate in ICR mice … the increased incidence of malignant tumors in the highest-dose group of prepubertal C3Han/f mice was assumed to be due not to a direct carcinogenic effect of melengestrol acetate but to the promoting effect of increased prolactin concentrations'."[903]

7.808 Dr. Boisseau's comment is confirmed by Dr. Boobis, referring *inter alia* to study 4 of the 17 studies commissioned by the European Communities:

> "There is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic. They were negative in a range of tests for genotoxicity. They were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. Trenbolone also produced a low level of DNA adducts measured by 32P-post-labelling *(Metzler and Pfeiffer, 2001)*.[904] As indicated above, micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. In no case did any of the compounds produce a mutagenic response. These data are insufficient to support the conclusion that these hormones have genotoxic potential in vivo. Thus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo."

7.809 Dr. Guttenplan also agreed that:

> "[T]here is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential. There is some evidence that certain of the hormones have genotoxic potential, but generally the potential is weak. ... MGA is negative in genotoxicity assays. Any

[902] 2002 Opinion, section 4.5.3, p. 18. The general conclusions, states that "[d]ata on the genotoxicity of melengestrol acetate indicate only weak effects", p. 22.

[903] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 161.

[904] Dr. Boobis cited to Metzler M and Pfeiffer E (2001). Genotoxic potential of xenobiotic growth promoters and their metabolites. APMIS, **109**:89-95. See Annex D, para. 198.

> genotoxic effects of the five hormones are likely to be minimized by good veterinary practice."[905]

7.810 We note that the European Communities argues that new studies have brought fresh evidence which depart from the majority view. At our request, the experts commented on the 17 studies commissioned by the European Communities. Regarding study 4, which is referred to in the 2002 Opinion, Dr. Boobis confirmed the negative results concerning mutagenicity and genotoxicity of melengestrol acetate:

> "[I]n study 4 (mutagenicity and genotoxicity of MGA), MGA was negative in studies of the induction of *hprt* mutations in V79 cells, the induction of micronuclei in V79 cells and the induction of *lac*I mutations in *E coli*. Pure MGA had no effect on apoptosis, which could potentially confound interpretation of studies using V79 cells."[906]

7.811 Dr. Boobis adds, with respect to DNA adducts, that:

> "[P]reliminary studies with rat liver slices, reported in an abstract but not yet published in the peer reviewed literature, suggested that MGA could produce unidentified adducts with DNA. As indicated above, there are mechanisms of adduct formation that do not involve direct interaction of the inducing compound with DNA. Overall, a report of putative covalent binding to DNA observed using 32P-post-labelling is not sufficient to over-ride the consistently negative results of MGA in a range of tests for mutagenicity. Hence, on the basis of the findings in study 5, there is no reasons to change the risk assessment or MGA."[907]

7.812 Regarding carcinogenicity of melengestrol acetate, we note that melengestrol acetate has not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with this growth promotion hormone.[908] In reply to a question from the Panel on whether the carcinogenic effects of the hormones at issue were related to a mechanism other than hormonal activity, Dr. Boisseau replied that:

> "[i]n its 1999 report, SCVPH concluded, about the carcinogenicity of melengestrol, that: 'in view of the lack of data on mutagenicity/carcinogenicity and on DNA interactions and in consideration of carcinogenicity studies conducted only in one animal species, these data are inadequate to assess the carcinogenic potential of melengestrol.' Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of melengestrol are related to a mechanism other than hormonal activity."[909]

7.813 The European Communities contests these comments, arguing that Dr. Boisseau interprets lack of data as lack of adverse effect.[910] We do not agree with the European Communities. The test to be met under Article 5.7 is that relevant scientific evidence be insufficient, and we have considered that, in this case, this implied that there be a critical mass of new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make

[905] Reply of Dr. Guttenplan to question 21 of the Panel, Annex D, para. 200. Dr. Guttenplan, referring to the 2002 Opinion, mentioned that his reply for the hormones would not have been different in September 2003.

[906] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 486.

[907] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 486.

[908] IARC reply to question 25 of the Panel, Annex E-3, p. 129.

[909] Reply of Dr. Boisseau to question 16 of the Panel, Annex D, para. 162.

[910] EC's comments on the experts replies, question 16, Annex F-1, p. 13.

relevant, previously sufficient, evidence now insufficient. This is also the case for melengestrol acetate. We recall that JECFA evaluated this hormone on two occasions. This suggests that evidence has been at one point sufficient. Having regard to this context, we do not read the EC comment, nor any evidence presented in the course of these proceedings, as meeting the above-mentioned test.

Conclusion

7.814 Having regard to our specific conclusions above, we recall that the Appellate Body clarified in *Japan – Apples* that relevant scientific evidence will be insufficient within the meaning of Article 5.7 if the body of available scientific evidence does not allow, in quantitative or qualitative terms, the performance of an adequate assessment of risks as required under Article 5.1. In this respect, we note that, at our request, the experts also expressed their views on the more general question whether the scientific evidence available at the time of the adoption of Directive 2003/74/EC and subsequently allowed the conduct of a risk assessment, in relation to meat from cattle treated, *inter alia*, with melengestrol acetate. Dr. Boobis replied that:

> "[T]here was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue."

7.815 We also note Dr. Guttenplan's comment with respect to JECFA's risk assessment that:

> "The assessment for melengestrol acetate seems sound. Thorough metabolic and estrogenic studies have been carried out."[911]

7.816 These general remarks support our conclusions on the specific elements discussed above. We therefore conclude that it is not established that the relevant scientific evidence is insufficient with respect to melengestrol acetate, within the meaning of Article 5.7 of the *SPS Agreement*.

(xii) Conclusion

7.817 We recall that we asked the scientific experts whether the scientific evidence relied upon by the European Communities supports the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed.[912]

7.818 Three experts replied. In his written reply, Dr. Guttenplan saw several important gaps and gave examples. However, at the meeting with the Panel, he specified that, "on subsequent reading, [he] could not find anything to indicate adverse effect, and [he] now think[s] that risk assessment is alright."[913] He added that "the ability [to make a risk assessment] varies between compounds, but that does not mean you can't make a risk assessment, it just means the accuracy of the risk assessment is different."[914] The other two experts considered that "these new data [provided by the European Communities] [did] not demonstrate any important gaps, insufficiencies or contradictions in the scientific information used by JECFA for conducting its risk assessments" (Dr. Boisseau)[915], or that "[t]here was little information in the scientific studies initiated by the EC since 1997 that support the

[911] Reply of Dr. Guttenplan to question 61 of the Panel, Annex D, para. 458.
[912] Panel question 62.
[913] Transcript of the Panel meeting with the experts, Annex G, para. 981.
[914] Transcript of the Panel meeting with the experts, Annex G, para. 983.
[915] Reply of Dr. Boisseau to question 62 of the Panel, Annex D, para. 460.

contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat from treated animals can be assessed" (Dr. Boobis).[916] Dr. Boobis elaborated as follows:

> "Whilst additional information has been obtained on a number of aspects of the hormones in question, this was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded on previous knowledge. The evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion."

7.819 We also note that, at our meeting with experts, Dr. Cogliano and Dr. Boobis confirmed, in response to a question from the Panel, that the data were sufficient to perform a risk assessment based on ADI, as done by JECFA.[917]

7.820 We recall that the test we applied in this case was that there must be a critical mass of new evidence and/or information that calls into question the fundamental precepts of previous knowledge and evidence so as to make relevant, previously sufficient evidence now insufficient. We note that the experts who expressed themselves in detail on this matter have confirmed, both in general and for each of the five hormones subject to a provisional ban, that such critical mass had not been reached.

7.821 For all these reasons, we conclude that it has not been demonstrated that relevant scientific evidence was insufficient, within the meaning of Article 5.7 of the *SPS Agreement*, in relation to any of the five hormones with respect to which the European Communities applies a provisional ban.

7.822 We recall that all four of the requirements identified by the Appellate Body in *Japan – Agricultural Products II* with regard to the application of Article 5.7 of the *SPS Agreement* must be satisfied in order to adopt and maintain a provisional measure. The Appellate Body noted that the four requirements are "clearly cumulative in nature". Since we found that the first requirement (the measure is imposed in respect to a situation where "relevant scientific evidence is insufficient") has not been satisfied, we do not find it necessary to address any of the three other requirements. We therefore conclude that the EC compliance measure does not meet the requirements of Article 5.7 of the *SPS Agreement* as far as the provisional ban on progesterone, testosterone, zeranol, trenbolone acetate and melengestrol acetate is concerned.

7.823 Having reached that conclusion, we want to make clear that we only determined that it had not been established that the existing relevant scientific evidence was insufficient. This does not mean that no measure can be imposed by the European Communities under the *SPS Agreement* in relation to the five hormones at issue. Indeed, our determinations are without prejudice to the legality of any EC measure regarding these hormones, should the European Communities decide to complete its risk assessments pursuant to Article 5.1 of the *SPS Agreement*.

[916] Reply of Dr. Boobis to question 62 of the Panel, Annex D, para. 495.

[917] Transcript of the Panel meeting with the experts, Annex G, Dr. Cogliano, para. 871; Dr. Boobis, para. 873.

(g) Compatibility of the EC implementing measure with Article 3.3 of the *SPS Agreement* with respect to all hormones with the exception of melengestrol acetate

Summary of the main arguments of the parties[918]

7.824 **Canada** argues that WTO Members are allowed under Article 3.3 of the *SPS Agreement* to maintain SPS measures that result in a higher level of protection than that which would otherwise be achieved through measures that are based on international standards only if certain conditions are met.

7.825 Canada notes that the European Communities permanent ban on oestradiol-17β and its provisional ban on the other five hormones result in a level of protection that is higher than that implied in international standards. On the basis of conclusions by JECFA that the presence of hormone residues in meat from treated animals does not present a health concern, Codex established MRLs for trenbolone acetate and zeranol, and decided that none was necessary for oestradiol-17β, testosterone and progesterone.

7.826 Therefore, not only must the European Communities demonstrate, pursuant to Article 5.1 of the *SPS Agreement*, that its measure is "based on" a risk assessment, but the risk assessment on which the EC measure is based must also demonstrate that existing international standards (*i.e.* the ADI and MRLs established by JECFA and Codex) are not capable of achieving "zero additional risk" – the appropriate level of protection that the European Communities has set for itself. Canada considers that The European Communities failed to identify any "additional risks" that would arise from ingestion of residues of the six hormones at levels that comply with international standards. As a result of this failure, the EC measure is also inconsistent with Article 3.3 of the *SPS Agreement.*[919]

7.827 The **European Communities** argues that it decided not to use the Codex standard on oestradiol-17β, because the Codex recommendations are not only old but also do not allow the European Communities to achieve the level of protection it considers appropriate in its territory.[920]

7.828 With respect to the other five hormones, the European Communities considers that it is possible, in the presence of an international standard, guideline or recommendation that is based on a risk assessment, to adopt a provisional sanitary measure on the grounds that the relevant scientific evidence is insufficient. A Member may disagree with the risk assessment for scientific reasons and, in particular, on the issue of whether the scientific evidence relied upon is sufficient. Such disagreement may stem from differences of views on scientific questions such as methodology, data interpretation etc. It may also result from the fact that in order to meet a higher level of protection, the Member concerned may require more information than what is provided in the risk assessment in question. As a concrete example, the JECFA study referred to by the defending parties did not take into account the data obtained in the seventeen studies which had been performed upon the initiative and with the funding of the European Communities.[921]

[918] A more detailed account of the parties' arguments can be found in Section IV of the descriptive part of this Report. The order in which the respective arguments of the parties are presented does not reflect any allocation of the burden of proof by the Panel.

[919] Canada's second written submission, paras. 51-54.

[920] EC's replies to Panel questions after the first substantive meeting, question 22, Annex B-1, para. 129,; EC's second written submission, para. 101; EC's oral statement at the second panel meeting (20 October 2006), para. 19.

[921] EC's replies to Panel questions after the first substantive meeting, question 72, Annex B-1.

Reasoning of the Panel

7.829 Article 3.3 of the *SPS Agreement* reads as follows:

> "Members may introduce or maintain sanitary ... measures which result in a higher level of sanitary ... protection than would be achieved by measures based on the relevant international standards, guidelines or recommendations, if there is a scientific justification, or as a consequence of the level of sanitary ... protection a Member determines to be appropriate in accordance with the relevant provisions of paragraphs 1 through 8 of Article 5.[922] Notwithstanding the above, all measures which result in a level of sanitary ... protection different from that which would be achieved by measures based on international standards, guidelines or recommendations shall not be inconsistent with any other provision of this agreement."

7.830 We concluded above that the European Communities did not comply with Article 5.1 and with Article 5.7 of the *SPS Agreement*. In light of our mandate and of our objectives in engaging in a review of the conformity of the EC implementing measure with the *SPS Agreement*, we see no reason to reach a conclusion on Article 3.3 of the *SPS Agreement*, to the extent that this conclusion depends on a violation of Article 5.

7.831 We therefore refrain from drawing any conclusion with respect to Article 3.3 of the *SPS Agreement*.

(h) Conclusion on Article 22.8 of the DSU

7.832 For the reasons stated above, we conclude that it has not been established that the European Communities has removed the measure found to be inconsistent with a covered agreement.

7.833 We also note that the European Communities does not claim that it has provided a solution to the nullification or impairment of benefits suffered by Canada within the meaning of Article 22.8 of the DSU.

7.834 None of the parties has claimed that a mutually satisfactory solution had been found in the context of the *EC – Hormones* case.

7.835 For these reasons and those developed above, we find that the European Communities did not demonstrate a breach of Article 22.8 of the DSU by Canada.

4. Violation of Articles 23.1 and 3.7 of the DSU

7.836 The Panel recalls its understanding that violations of Articles 23.1 and 3.7 were only claimed in relation to the violation of Article 22.8 of the DSU. To the extent that Article 22.8 has not been breached, the European Communities has not established a violation of Articles 23.1 and 3.7 of the DSU. The Panel concludes that there is no violation of Articles 23.1 and 3.7 of the DSU by Canada as a result of a breach of Article 22.8.

[922] (*footnote original*) For the purpose of paragraph 3 of Article 3, there is a scientific justification if, on the basis of an examination and evaluation of available scientific information in conformity with the relevant provisions of this agreement, a Member determines that the relevant international standards, guidelines or recommendations are not sufficient to achieve its appropriate level of sanitary ... protection.

D. VIOLATION OF ARTICLE I:1 AND ARTICLE II OF THE GATT 1994

7.837 The European Communities has claimed that there is a violation of Articles I:1 and II of the GATT 1994 because Canada's continued suspension of obligations could not be justified anymore under Article 22 of the DSU.

7.838 In light of our conclusions above, we see no basis to make findings in relation to these claims.

E. CONDITIONAL CLAIM OF VIOLATION OF ARTICLE 22.8 OF THE DSU MADE IN THE ALTERNATIVE

7.839 We recall that the European Communities also raised a *conditional* claim of violation of Article 22.8 of the DSU *per se*. The European Communities specified in its first written submission that this claim was "made in the alternative and only on the condition that the Panel does not establish any violation under Articles 23.1, 23.2(a), 3.7, 22.8 and 21.5 of the DSU".[923]

7.840 We note that we have established a violation of Article 23.1 and 23.2(a). We also recall that we have already addressed the alleged violation of Article 22.8 of the DSU as part of our review of the EC claim of violation of Article 23.1 read together with Article 22.8 and Article 3.7 of the DSU. Under those circumstances, it is not necessary for the Panel to address the conditional claim of violation 22.8 of the DSU *per se* in the alternative.

F. CONCLUSION

7.841 For the reasons set forth in this report, the Panel concludes that, with respect to the claims of the European Communities concerning the violation of Article 23.2(a) read together with Articles 21.5 and 23.1 of the DSU, Canada made the following procedural violations:

(a) by seeking, through the measure at issue – that is the suspension of concessions or other obligations subsequent to the notification of the EC implementing measure (Directive 2003/74/EC) – the redress of a violation of obligations under a covered agreement without having recourse to, and abiding by, the rules and procedures of the DSU, Canada has breached Article 23.1 of the DSU;

(b) by making a determination within the meaning of Article 23.2(a) of the DSU to the effect that a violation had occurred without having recourse to dispute settlement in accordance with the rules and procedures of the DSU, Canada has breached Article 23.2(a) of the DSU.

7.842 In addition, having addressed the claims raised by the European Communities concerning the violation of Article 23.1 read together with Articles 22.8 and 3.7 of the DSU based on the considerations mentioned above[924], the Panel concludes that,

(a) to the extent that the measure found to be inconsistent with the *SPS Agreement* in the *EC – Hormones* dispute (WT/DS48) has not been removed by the European Communities, Canada has not breached Article 22.8 of the DSU;

(b) to the extent that Article 22.8 has not been breached, the European Communities has not established a violation of Articles 23.1 and 3.7 of the DSU *as a result of a breach of Article 22.8*.

[923] EC's first written submission, para. 133.
[924] See Section VII.C.2 and Section VII.C.3(a), (b) and (c) above.

VIII. RECOMMENDATIONS

8.1 Article 3.8 of the DSU provides that "[i]n cases where there is an infringement of the obligations assumed under a covered agreement, the action is considered prima facie to constitute a case of nullification or impairment". Canada failed to rebut this presumption. Therefore, to the extent Canada has acted inconsistently with its obligations under the DSU, it must be presumed to have nullified or impaired benefits accruing to the European Communities under that Agreement.

8.2 In the light of these conclusions, the Panel recommends that the Dispute Settlement Body request Canada to bring its measure into conformity with its obligations under the DSU.

8.3 Whereas it is for the Members to decide on the appropriate steps needed to bring measures found in breach of their WTO obligations into conformity, the Panel deems it important to recall its conclusion in paragraph 7.244 above as the parties have apparently diverging opinions as to how this report should be implemented by the respondent. As already mentioned, while the Panel performed functions similar to that of an Article 21.5 panel, this was done only in order to determine whether Article 22.8 of the DSU had been breached. This Panel was not called upon, nor does it have jurisdiction, to determine the compatibility of Directive 2003/74/EC with the covered agreements. In that context, the Panel suggests that, in order to implement its findings under Article 23 and in order to ensure the prompt settlement of this dispute, Canada should have recourse to the rules and procedures of the DSU without delay.

WORLD TRADE ORGANIZATION

WT/DS321/R/Add.1
31 March 2008

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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex A to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex B: Add.2
- Annex C: Add.3
- Annex D: Add.4
- Annex E: Add.5
- Annex F: Add.6
- Annex G: Add.7

ANNEX A

CORRESPONDENCE FROM THE PANEL TO THE PARTIES AND WORKING PROCEDURES

ANNEX A-1

LETTER TO THE PARTIES DATED 1 AUGUST 2005 ON THE PANEL DECISION ON OPEN HEARINGS FOR PUBLIC OBSERVATION

In light of the parties' common request made on 13 June 2005 to have their meetings with the Panel open to the public; keeping in mind the Panel's obligation to ensure that its Working Procedures are objective, impartial and non-discriminatory; and after careful consideration of the existing provisions of the DSU and its Appendix 3, the Panel has decided to accept the parties' request and to agree that the panel meetings at which the parties are invited to appear, as referred to in paragraph 2 of Appendix 3 of the DSU, will be open for observation by the public through a closed-circuit broadcast.

With a view to ensuring transparency to the fullest extent possible and non-discriminatory access by all people, in particular by all Members, the Panel will request the Secretariat to finalize the appropriate logistical arrangements, and to guarantee that each WTO Member delegation has at least two seats available in the room where the closed-circuit broadcast will be transmitted. In addition, before its second meeting with the parties, the Panel will review the need to extend further such non-discriminatory access, through internet broadcasting, in light, *inter alia*, of the interest shown by and comments received from the public and taking into consideration any relevant information provided by the Secretariat relating to this matter.

Since not all third parties have agreed that their session with the Panel be open for observation by the public, that session will remain closed.

Please note that, as provided in paragraph 3 of the Panel's Working Procedures, the parties retain the right to request at any time, including during panel meetings at which they are invited to appear, that specific statements of theirs not be broadcast so as to remain confidential. The Panel may also decide on its own to suspend broadcasting at any time, including during such meetings.

Finally, the Panel wishes to bring to the attention of the parties that the dates of the first meeting of the Panel with the parties and third parties have been changed as follows: On Monday and Tuesday, 12 and 13 September, the Panel will meet with the parties; on Wednesday morning, 14 September, the Panel will meet with the third parties; and on Thursday 15 September, the Panel will meet again with the parties to complete its first substantive meeting and allow parties, if need be, to present their closing statements.

The Panel reserves the right to elaborate further in its report on its reasoning with regard to this decision.

Attached is a revised version of the Working Procedures and a revised Timetable of the Panel that reflect this decision.

ANNEX A-2

WORKING PROCEDURES FOR THE PANEL

1. The Panel will provide the parties with a timetable for panel proceedings and will work according to the normal working procedures as set out in the DSU and its Appendix 3 plus certain additional procedures, as follows:

2. The Panel shall meet in closed session. The parties to the dispute, and the third parties, shall be present at the meetings only when invited by the Panel to appear before it. In light of the parties' common request, the panel meetings at which the parties are invited to appear will be open for observation by the public through closed-circuit broadcast, provided satisfactory logistical arrangements can be maintained by the Secretariat.

3. At any moment including during such meetings, any party may request the Panel to suspend the broadcasting for as long as necessary in order to protect confidentiality. The Panel also has the right on its own to suspend the broadcasting at any time, including during such meetings.

4. The deliberations of the Panel and the documents submitted to it shall be kept confidential. Nothing in these procedures shall preclude a party to a dispute from disclosing statements of its own positions to the public, provided that that party does not thereby disclose any confidential information from the other parties or third parties. Members shall treat as confidential information submitted by another Member to the Panel which that Member has designated as confidential. As provided in Article 18.2 of the DSU, where a party to a dispute submits a confidential version of its written submissions to the Panel, it shall also, upon request of a Member, provide a non-confidential summary of the information contained in its submissions that could be disclosed to the public.

5. Before the first substantive meeting of the Panel with the parties, the parties to the dispute shall transmit to the Panel written submissions in which they present the facts of the case and their arguments. The third parties may transmit to the Panel written submissions after the first written submissions of the parties have been submitted.

6. At its first substantive meeting with the parties, the Panel shall ask the party which has brought the complaint to present its case. Subsequently, at the same meeting, the party against which the complaint has been brought shall be asked to present its points of view.

7. The third parties shall be invited in writing to present their views during a session of the first substantive meeting of the Panel set aside for that purpose. In light of the absence of a common agreement among the third parties on the issue of opening this session of the panel meeting for observation by the public, this session will remain closed. The third parties may be present during the entirety of this session.

8. Formal rebuttals shall be made at the second substantive meeting of the Panel. The party complained against shall have the right to take the floor first to be followed by the complaining party. The parties shall submit, prior to that meeting, written rebuttals to the Panel.

9. The Panel may at any time put questions to the parties and ask them for explanations either in the course of a meeting with the parties or in writing. Written replies to questions shall be submitted by the date(s) decided by the Panel

10. The parties to the dispute and any third party invited to present its views shall make available to the Panel and to the parties a written version of their oral statements.

11. The presentations, rebuttals and statements referred to in paragraphs 6 to 10 shall be made in the presence of the parties. Moreover, each party's written submissions, including responses to questions put by the Panel, comments on the descriptive part of the report, and comments on the interim report, shall be made available to the other party.

12. Any request for a preliminary ruling (including rulings on jurisdictional issues) to be made by the Panel shall be submitted no later than in a party's first written submission. If a party requests such a ruling, the other party shall submit its respective response(s) to such request within a time limit specified by the Panel. Exceptions to this procedure will be granted upon a showing of good cause.

13. The parties shall submit all factual evidence to the Panel no later than during the first substantive meeting, except with respect to evidence necessary for purposes of rebuttals, and answers and comments to questions. Exceptions to this procedure will be granted upon a showing of good cause. In such cases, the other parties shall be accorded a period of time for comment, as appropriate.

14. To facilitate the maintenance of the record of the dispute, and for ease of reference to exhibits submitted by the parties, parties are requested to number their exhibits sequentially throughout the stages of the dispute.

15. The parties and third parties shall endeavour to provide the Panel with executive summaries of the facts and arguments as presented to the Panel in their written submissions and oral statements within 10 days following the delivery to the Panel of the relevant written submissions or oral statements. The executive summaries of the written submissions to be provided by each party should not exceed 10 pages in length each and the executive summaries of the oral statements should not exceed 5 pages in length each.

16. The executive summaries shall not in any way serve as a substitute for the submissions of the parties in the Panel's examination of the case. However, the Panel may reproduce the executive summaries provided by the parties and third parties in the arguments section of its report, subject to any modifications deemed appropriate by the Panel. The parties' and third parties' replies to questions, and the parties' comments on each other's replies to questions may be attached to the Panel report as annexes.

17. The parties and third parties to these proceedings have the right to determine the composition of their own delegations. The parties and third parties shall have responsibility for all members of their delegations and shall ensure that all members of their delegations act in accordance with the rules of the DSU and the Working Procedures of this Panel. The parties shall provide a list of the participants of their delegation before or at the beginning of the meeting with the Panel.

18. Following issuance of the interim report, the parties shall have no less than 10 days to submit written requests to review precise aspects of the interim report and to request a further meeting with the Panel. The right to request such a meeting must be exercised no later than at the time the written request for review is submitted. Following receipt of any written requests for review, in cases where no further meeting with the Panel is requested, the parties shall have the opportunity within one week to submit written comments on the other party's' written requests for review. Such comments shall be strictly limited to commenting the other party's written requests for review.

19. The following procedures regarding service of documents apply:

(a) Each party and third party shall serve its submissions directly on all other parties, including where appropriate the third parties, and confirm that it has done so at the time it provides its submissions to the Panel.

(b) The parties and third parties should provide the Panel and the parties with their submissions, answers to questions and comments invited by the Panel by 5:30 p.m. on the deadline dates established by the Panel, unless a different time is set by the Panel.

(c) The parties and third parties shall provide the Panel and the parties with copies of their oral statements, preferably at the end of the meeting, and in any event not later than noon of the first working day following the last day of the substantive meetings. The parties and third parties are encouraged to provide a provisional written version of their oral statements at the time the oral statement is presented.

(d) The parties and third parties shall provide the Panel with 9 hard copies of all their submissions, including the written versions of oral statements and answers to questions. All these copies shall be filed with the Dispute Settlement Registrar, ***** (office number 3154).

(e) At the time they provide a hard copy of their submissions, the parties and third parties shall also provide the Panel with an electronic copy of all their submissions on a diskette or as an e-mail attachment in a format compatible with the Secretariat's software. E-mail attachments shall be sent to the Dispute Settlement Registry (DSRegistry@wto.org) with a copy to ***** (e-mail: *****@wto.org), Secretary to the Panel.

(f) Each party shall serve executive summaries mentioned in paragraph 15 directly on the other parties, and third parties when relevant, and confirm that it has done so at the time it provides its submission to the Panel. Each third party shall serve executive summaries mentioned in paragraph 15 directly on the parties and other third parties and confirm that it has done so at the time it provides its submission to the Panel. Subparagraphs (d) and (e) above shall be applied to the service of executive summaries.

20. The Panel reserves the right to modify these procedures at any time following consultations with the parties.

ANNEX A-3

LETTER TO THE PARTIES DATED 20 OCTOBER 2005 ON THE PANEL DECISION ON CONSULTING SCIENTIFIC AND TECHNICAL EXPERTS

The Panel has instructed me to communicate the following message to you.

The Panel recalls that it sought the opinions of the Parties on whether there was a need to consult technical or scientific experts on sanitary issues, should the Panel consider it necessary in the process of resolving this dispute. From the Parties' replies to the questions of the Panel, it appears that no Party disagrees that, should the Panel proceed with an assessment of the measure taken by the European Communities to comply with the recommendations and rulings of the DSB in the *EC – Hormones* case (hereafter the "EC implementing measure"), advice from technical or scientific experts would be necessary.

The Panel notes the views expressed by the European Communities regarding the nature of this case and the order in which its claims should be reviewed by the Panel. At this early stage, the Panel is of the view that it is in its interest, as well as in the interest of the Parties, to be fully informed of all relevant aspects of the dispute before it reaches a decision.

As a result, in order to facilitate the smooth handling of the proceedings while ensuring that Parties are given ample opportunities to express their views on all aspects of the case, the Panel has decided to initiate a process for consultation with experts in relation to the technical or scientific aspects of the compatibility of the EC's implementing measure with the relevant provisions of the SPS Agreement.

The Panel would like to stress that the decision to proceed with the consultation with experts is without prejudice to the positions held by any Party in this respect and without prejudice to the conclusions that the Panel will ultimately reach on the claims raised by the European Communities.

Attached for your consideration and comments, if any, are (i) the working procedures the Panel proposes to use for consultations with experts and (ii) a revised timetable reflecting the necessary adjustments resulting from the incorporation of an expert consultation process in these proceedings.

You will note from the attached timetable that in light of this decision, the Panel considers it appropriate to grant to all Parties a further extension of the deadline for submitting rebuttals, until Wednesday,16 November 2005. Furthermore, the date of the second substantive meeting of the Panel with the Parties will be postponed to the week beginning on 13 March 2006.[1] Should a meeting with the experts be considered necessary, the Panel would intend to hold that meeting immediately prior to the second substantive meeting with the Parties.

[1] The Panel recalls that a potential date for the second substantive meeting had been set for 6 December 2005. However, it was brought to the attention of the Panel in the meantime that the preparation and holding of the Ministerial Conference would make it quite impossible to hold any panel meeting before January 2006.

The Panel would appreciate your comments and/or suggestions by close of business on Tuesday, 25 October 2005 (i) on the attached proposed working procedures, (ii) on the technical or scientific aspects on which you would like the Panel to consult experts, (iii) on the adjustments made in the revised Panel timetable as well as (iv) on whether the meeting with the experts and the parties should be open for observation by the public.

ANNEX A-4

LETTER TO THE PARTIES DATED 25 NOVEMBER 2005 ON THE PANEL DECISION ON CERTAIN ISSUES CONCERNING THE EXPERTS' WORKING PROCEDURES

The Panel thanks the Parties for their comments on the expert working procedures and related issues, complemented by additional letters in response to points raised in each other's communications.

Having considered the extensive comments from the Parties on the expert consultation process, the Panel wishes to inform the Parties of its decision. The modified working procedures for seeking expert advice are attached.

Nature of Advice

The Panel will take into account the rebuttals before finalizing the issues for expert consultations.

Selection of experts

With respect to the EC's suggestion that the Panel seek advice from an expert review group instead of individual experts, the Panel is not convinced that this is a preferable option. Firstly, the Panel would wish to hear any dissenting or minority views among the experts rather than receiving a consensus text from an expert review group. We do not consider that the risk that experts may have diverging opinions would generate difficulties as serious as alleged by the EC. We see rather the risk that an expert review group would only agree on a minimum common position, thus depriving the Panel of a full picture. In addition, the fields of competence proposed by the Parties are quite varied, rendering it difficult to find individual experts which have competence in most or all of these fields to serve in an expert group. The fact that no expert will have a comprehensive knowledge of all the relevant subjects makes it even more important for the Panel to seek advice from the experts on an individual basis on their respective fields of expertise. It is also worth noting that so far, all WTO panels have preferred to consult experts on an individual basis.

The Panel also wishes to clarify that it will initially seek suggestions for experts from the Codex Alimentarius Commission, JECFA and the IARC and may also contact these three organizations with questions on their working procedures and/or their work in areas relevant to the dispute. Should the Panel consider it necessary to consult any other relevant organization, it will provide the Parties with an opportunity to comment prior to undertaking such consultations.

Having considered the EC's proposals that the Parties provide suggestions for experts and that the Panel exclude from consideration those who have received funding from pharmaceutical companies and/or been involved in the regulatory approval of hormones, the Panel has modified the expert working procedures to reflect some of the underlying concerns the EC might have. When contacting the experts suggested by international organizations, the Panel will underline the importance of disclosing information regarding any potential conflict of interest and elaborate more precisely the type of information that needs to be disclosed. Still, rather than ruling out any expert from the start, the Panel wishes to consider each expert's case individually, taking into account information provided by the experts and the comments provided by the Parties on these experts.

Should the Parties submit objections, which the Panel deems compelling, to all or most experts suggested, it will then seek additional suggestions for experts from other international organizations and, if deemed necessary, from the Parties.

Written Procedure

The Panel also wishes to confirm that a cover letter will accompany the questions to experts, explaining their role and mandate as well as their obligations in terms of potential conflicts of interest and confidentiality.

Meeting with Experts

The experts will be provided with an opportunity to respond to Parties' written comments on their replies during the meeting with the experts.

Further to affirmative statements from all Parties, the meeting with the experts will be open for observation by the public through closed-circuit television.

Other matters

With respect to the EC's request that the Panel ask the US and Canada to provide the studies underlying the risk assessments of the US, Canada (and JECFA), the Panel is not in a position to fully assess the necessity for this information at this stage. This said, the Panel notes that its task is not to conduct a comprehensive assessment of the safety of hormones in meat. Rather, should the Panel consider it necessary for the resolution of the present dispute, it would assess the compatibility of the EC's measure with the provisions of the SPS Agreement. Nevertheless, to the extent that this information becomes necessary for the Panel to make its determination in this case, the Panel cannot exclude that it may request part or all of the information referred to by the EC. More generally, the Panel expects the Parties' full collaboration in gathering the information necessary for an objective assessment of the matter before it. The Panel also recalls that it is for each party to submit sufficient evidence in support of its assertions.

Finally, the Panel wishes to remind the Parties that the main Working Procedures for the Panel also apply to the consultation with scientific experts.

ANNEX A-5

WORKING PROCEDURES FOR CONSULTATIONS WITH SCIENTIFIC AND/OR TECHNICAL EXPERTS

NATURE OF ADVICE

1. On the basis of the first written submissions, the oral statements, the replies to Panel's questions, and the rebuttals, the Panel will determine the areas in which it intends to seek expert advice

SELECTION OF EXPERTS

2. In consultation with the parties, the Panel will choose experts and seek their advice as individual experts. If it deems necessary, the Panel may also seek information and advice from the Joint FAO/WHO Codex Alimentarius Commission (CAC), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or the International Agency for Research on Cancer (IARC), or any other relevant international organization.

3. The Panel will solicit suggestions from the secretariats of CAC, JECFA and IARC for possible experts.

4. The Panel will seek a *curriculum vitae*, including all relevant publications, from each individual suggested. The candidate experts will also be asked to provide information about potential conflicts of interest and indications on whether they have worked for, been funded by or provided advice to the industries concerned, or to domestic or international regulatory bodies involved in issues similar to those addressed in this dispute. A list of eligible experts, including their *curricula vitae* and declarations of interest will be provided to the parties. Parties will have sufficient time to examine them and will be given the opportunity to comment on and to make known any compelling objections to any particular expert.

5. The Parties will receive copies of the Panel's correspondence with the relevant international organizations and the experts.

6. Should the Parties submit objections, which the Panel deems compelling, to all or most experts suggested by the CAC, JECFA, and the IARC, the Panel will seek additional suggestions for experts from other international organizations with competence in the matter and, if it deems it necessary, from the Parties.

7. The Parties are requested not to engage in direct contact in connection with this dispute with the individuals suggested.

8. The number of experts that the Panel will select will be determined in light of the number and types of issues on which advice will be sought, as well as by the different areas on which each expert can provide expertise.

9. After having reviewed the comments made by the Parties, experts will be appointed on the basis of their qualifications and the need for specialized scientific or technical expertise.

10. The Panel will inform the Parties of the experts it has selected.

11. The selected experts shall act in their individual capacities and not as representatives of any entity. They shall be subject to the *Rules of Conduct for the Understanding on Rules and Procedures Governing the Settlement of Disputes* (WT/DSB/RC1), including the self-disclosure requirement set out in Section VI of the rules of conduct.

WRITTEN PROCEDURE

12. The Panel will prepare specific written questions for the experts. Parties will have the opportunity to comment on the proposed questions, or suggest additional ones, before the Panel decides on the final questions to be sent to the experts.

13. The experts will be provided with the Parties' and third parties' written and oral submissions as well as their replies to the Panel's questions (including exhibits) on a confidential basis.[1] They will also be provided with the Panel and Appellate Body Reports on *European Communities – Measures Concerning Meat and Meat Products* (*EC – Hormones* – WT/DS26 and WT/DS48*).*

14. The experts will be requested to provide responses in writing within a time-period specified by the Panel. Copies of these written responses will be provided to the Parties. The Parties will have sufficient opportunities to comment in writing on the responses from the experts.

15. The Panel will ensure that: (i) the Parties' comments on the experts' responses are provided to the experts; (ii) the experts are individually provided with the other experts' responses to the Panel's questions.

16. Without prejudice to Paragraph 13 of the Panel Working Procedures on submission of evidence, and in order to facilitate the expert consultations, the Parties are requested to provide any scientific evidence which they believe would be useful for the experts by Monday, 21 December 2005.

MEETING WITH EXPERTS

17. The Panel intends to schedule a meeting with the experts prior to the second substantive meeting. A date for the meeting will be agreed in consultation with the Parties. During the meeting, the experts will be invited to present their replies to written and oral questions, complement these as necessary, respond to comments from the Parties on their written replies, and respond to additional questions from the Panel and the Parties. The Parties will be given an opportunity to ask questions they consider necessary in order to clarify the technical/scientific issues at stake.

18. In consultation with the Parties, the Panel will schedule additional meetings with the experts if it deems it appropriate.

19. The Parties are free to include scientific experts in their delegations.

20. The Secretariat will prepare a summary of experts' written replies to the Panel's questions, as well as a transcript of the meeting with the experts, for attachment as a supplement to the Panel's report. The experts and the Parties will be given sufficient time to comment on the drafts of these texts before they are finalized.

[1] This is without prejudice to the right of parties to make public any of their submissions or statements before the Panel.

21. The meeting with the experts will be open to observation by the public in the same manner as the other substantive meetings of the Panel.

WORLD TRADE ORGANIZATION

WT/DS321/R/Add.2
31 March 2008

(08-0909)

Original: English

CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex B to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex C: Add.3
- Annex D: Add.4
- Annex E: Add.5
- Annex F: Add.6
- Annex G: Add.7

ANNEX B

REPLIES OF THE PARTIES TO QUESTIONS POSED BY THE PANEL AND OTHER PARTIES AFTER THE FIRST SUBSTANTIVE MEETING

ANNEX B–1

REPLIES OF THE EUROPEAN COMMUNITIES TO QUESTIONS POSED BY THE PANEL AFTER THE FIRST SUBSTANTIVE MEETING

(3 October 2005)

TABLE OF CASES

Short Title	Full Case Title and Citation
Australia – Salmon	Appellate Body Report, *Australia – Measures Affecting Importation of Salmon*, WT/DS18/AB/R, adopted 6 November 1998, DSR 1998:VIII, 3327
Brazil – Aircraft	Appellate Body Report, *Brazil – Export Financing Programme for Aircraft*, WT/DS46/AB/R, adopted 20 August 1999, DSR 1999:III, 1161
Canada – Aircraft (Article 21.5 – Brazil)	Panel Report, *Canada – Measures Affecting the Export of Civilian Aircraft – Recourse by Brazil to Article 21.5 of the DSU*, WT/DS70/RW, adopted 4 August 2000, as modified by the Appellate Body Report, WT/DS70/AB/RW, DSR 2000:IX, 4315
EC – Export Subsidies on Sugar	Appellate Body Report, *European Communities – Export Subsidies on Sugar*, WT/DS265/AB/R, WT/DS266/AB/R, WT/DS283/AB/R, adopted 19 May 2005
EC – Hormones	Appellate Body Report, EC *Measures Concerning Meat and Meat Products (Hormones)*, WT/DS26/AB/R, WT/DS48/AB/R, adopted 13 February 1998, DSR 1998:I, 135
EC – Sardines	Appellate Body Report, *European Communities – Trade Description of Sardines*, WT/DS231/AB/R, adopted 23 October 2002
India – Patents (US)	Appellate Body Report, *India – Patent Protection for Pharmaceutical and Agricultural Chemical Products*, WT/DS50/AB/R, adopted 16 January 1998, DSR 1998:I, 9
Japan – Apples (Article 21.5 – US)	Panel Report, *Japan – Measures Affecting the Importation of Apples, Recourse to Article 21.5 of the DSU by the United States*, WT/DS245/RW, 23 June 2005
Korea – Procurement	Panel Report, *Korea – Measures Affecting Government Procurement*, WT/DS163/R, adopted 19 June 2000, DSR 2000:VIII, 3541
US – Certain EC *Products*	Appellate Body Report, *United States – Import Measures on Certain Products from the European Communities*, WT/DS165/AB/R, adopted 10 January 2001
US – FSC	Appellate Body Report, *United States – Tax Treatment for "Foreign Sales Corporations"*, WT/DS108/AB/R, adopted 20 March 2000, DSR 2000:III, 1619
US – FSC (Article 21.5 II – EC)	Appellate Body Report, *United States – Tax Treatment for "Foreign Sales Corporations" – Recourse to Article 21.5 of the DSU by the European Communities*, WT/DS108/AB/RW2, not yet adopted
US – Hot-Rolled Steel	Appellate Body Report, *United States – Anti-Dumping Measures on Certain Hot-Rolled Steel Products from Japan*, WT/DS184/AB/R, adopted 23 August 2001, DSR 2001:X, 4697
US – Offset Act (Byrd Amendment)	Appellate Body Report, *United States – Continued Dumping and Subsidy Offset Act of 2000*, WT/DS217/AB/R, WT/DS234/AB/R, adopted 27 January 2003
US – Shrimp	Appellate Body Report, *United States – Import Prohibition of Certain Shrimp and Shrimp Products*, WT/DS58/AB/R, adopted 6 November 1998, DSR 1998:VII, 2755
US – Wool Shirts and Blouses	Panel Report, *United States – Measure Affecting Imports of Woven Wool Shirts and Blouses from India*, WT/DS33/R, adopted 23 May 1997, as upheld by the Appellate Body Report, WT/DS33/AB/R, DSR 1997:I, 343

Q1. In their first submissions, Canada and the United States argue that the European Communities could have had recourse to Article 21.5 of the DSU. Could the EC explain why it did not have recourse to Article 21.5 of the DSU? Did the EC consider seeking a decision of the DSB abrogating the authorization to suspend concessions or other obligations granted to Canada and the United States by the DSB on 26 July 1999? If not, why?

1. The European Communities considers that an implementing Member cannot have recourse to Article 21.5 of the DSU in order to confirm the WTO-consistency of its compliance measure. The European Communities has already explained that the dispute settlement system is based on contradictory proceedings where a WTO Member claims the *inconsistency* of a measure of another WTO Member. On the other hand, the dispute settlement proceeding is not appropriate to request an abstract confirmation of the *consistency* of a measure.[1]

2. This understanding is confirmed by the very notion of the DSU as a "dispute" settlement system. Moreover, this basic logic is also reflected in Articles 1.1, 3.3, 3.12, 4.4, 4.7 and 6 of the DSU.

3. The WTO dispute settlement system is based on the "Understanding on Rules and Procedures Governing the Settlement of Disputes". The word "dispute" indicates that the WTO proceedings are designed to resolve differences between WTO members. Thus, the *New Shorter Oxford English Dictionary* defines a "dispute", *inter alia*, as "a disagreement in which opposing views are strongly held".[2]

4. Consequently, the DSU is not designed to seek an abstract confirmation of the WTO-consistency of a measure in the absence of a challenge by another Member. Unlike other legal systems, the DSU does not provide for an objective procedure whereby a WTO Member could ask a Panel for an opinion about its measure.

5. The structure and the definition of the scope of application of the DSU confirm this principle. Under Article 1.1, the DSU

> (…) shall apply to disputes brought pursuant to the consultation and dispute settlement provisions of the (…) [covered] agreements (…). The rules and procedures of this Understanding shall also apply to consultations and the settlement of disputes between Members concerning their rights and obligations under the provisions of (…) this Understanding.

6. Thus, it is clear that the assertion "there is WTO-consistency (notably with the *SPS Agreement*)" would not be a "dispute" related to rights and obligations under the DSU, but one related to rights and obligations under the *SPS Agreement*. It would also not be possible to consider this as a basis for a "dispute" under Article 11.1 of the *SPS Agreement* and Article XXIII:1(a), (b) or (c) of the GATT. Therefore, the European Communities does not even see how the DSU would apply to such a self-initiated procedure under Article 21.5 of the DSU.

7. Article 3.3 of the DSU further confirms that the dispute settlement system is based on contradictory proceedings. Article 3.3 provides that:

> The prompt settlement of situations in which a Member considers that *any benefits accruing to it directly or indirectly under the covered agreement are being impaired by measures taken by another Member* is essential to the effective functioning of the

[1] EC Oral Statement, para. 54.
[2] *The New Shorter Oxford English Dictionary*, Vol. 1, 1993, p. 701.

> WTO and the maintenance of a proper balance between the rights and obligations of Members. (Emphasis added)

8. Thus, Article 3.3 assumes a scenario where one Member challenges the measure of another Member because the complaining member considers its rights being affected. Conversely, Article 3.3 does not address the situation where a Member is complaining against its own measure. In fact, unless one assumes that WTO members act in a schizophrenic manner they would not consider that "any benefits accruing to it (…) are being impaired".

9. Furthermore, Articles 6, 3.12, 4.4 and 4.7 of the DSU have in common that they refer to a "complaining party" and/or "a complaint". The use of these terms demonstrates again that the DSU is based on contradictory proceedings.[3]

10. The term "complaining party" derives from the word "to complain" which is defined in the *New Shorter Oxford Dictionary* as "bewail, lament, express dissatisfaction, formal statement of a grievance, bring a charge".[4] The European Communities fails to see how a Member who seeks confirmation of the WTO-consistency of the measure could fall under this ordinary meaning of the word. Indeed, this WTO-Member would just do the opposite of "complaining" against its measure.

11. The European Communities would note that the notion of a "complaining party" logically also requires a "defending or responding party" (or in the words of the working procedures "the party complained against"). Even if one assumes for the sake of the argument that the European Communities could be a "complaining party" in a self-initiated Article 21.5 proceeding, the European Communities fails to see how the United States and Canada could be considered as "defending parties" or as "parties complained against". Certainly, the United States and Canada would not "defend" the EC's compliance measure. In the same vein, the European Communities would not consider the United States and Canada as parties against which it had brought a complaint against the EC compliance measure. Also, a self-initiated Article 21.5 dispute would not cover the retaliatory measures which the United States and Canada are applying against the European Communities, because these measures are not the "measures taken to comply" over whose existence or WTO-compatibility there is a disagreement.

12. In this context, the European Communities is also wondering whether the United States and Canada as "defending party" would be obliged to participate in such proceedings. Indeed, in the only ever self-initiated compliance proceeding (*EC – Bananas III – Article 21.5 (EC)*) the United States (and other original complainants) explicitly refused to do so and the panel stated that it was unable to force them to do so. Even in the current proceeding the United States did not explicitly confirm that it would participate in an Article 21.5 proceeding if self-initiated by the European Communities.

13. In similar vein, Articles 6, 3.12 and 4.4 refer to the term "*complaint*". This word is defined in the *New Shorter Oxford Dictionary* as "a lamentation, a plaint, a formal accusation or charge".[5] Yet, by requesting an Article 21.5 compliance Panel, the European Communities would not make "a plaint" or bring "a formal accusation or charge" against its own measure. Rather, the opposite is the case.

14. In this context, it is also relevant to consider the past practice of WTO members in Article 21.5 proceedings. Since the establishment of the WTO until August 2005 there have been sixteen Article 21.5-proceedings. Fifteen out of these sixteen proceedings had been initiated by the original complaining Party which disagreed with a compliance measure. All of these 15 proceedings

[3] *See* also Article 9 of the DSU on multiple complainants.
[4] *The New Shorter Oxford English Dictionary*, Vol. 1, 1993, p. 459.
[5] *The New Shorter Oxford English Dictionary*, Vol. 1, 1993, p. 459.

worked in that they resulted in violation findings or in findings that the compliance measure was not inconsistent with the invoked provisions. The only exception where the Article 21.5 proceeding has been initiated by the original respondent was the case *EC – Bananas III (Article 21.5 (EC))*. For the reasons already mentioned above, this proceeding did not work. Also, this report was never adopted and it has therefore no legal status. Rather the non-adoption of this report confirms that the WTO Members did not agree with the approach undertaken at the time by the European Communities. In the European Communities' view, this subsequent practice is relevant for the correct interpretation of Article 21.5 of the DSU in accordance with Article 31.3(b) of the Vienna Convention of the Law of the Treaties.

15. Finally, an Article 21.5 proceeding initiated by the European Communities would not affect the DSB authorization because an Article 21.5 panel only has jurisdiction to rule on the question of compliance. It would certainly not make sense to go through an Article 21.5 process in order to subsequently launch yet another case like the present one in order to challenge any continuing sanctions.

16. In respect of the second half of the question on whether the European Communities sought a DSB decision abrogating the DSB authorization, the answer is no. The DSU does not provide for a legal basis for the DSB to do so nor a decision-making procedure. For instance, Article 2 of the DSU (which defines the tasks of the DSB) only mentions the right of the DSB to authorize the suspension of concessions. But it does not address the withdrawal of the DSB authorization. Thus, as Article 2.4 of the DSU refers only to explicit provisions under which the DSB may take a decision and in the absence of such a provision regarding the withdrawal of the DSB authorization the European Communities did not pursue this road.

17. The European Communities would assume that the absence of any provision on the abrogation of a DSB authorization may be also one reason why in those cases where a DSB authorization has been granted this authorization has never been withdrawn.[6]

18. The only DSU provision dealing with an end of the sanctions is Article 22.8. Yet, as already explained this provision concerns the *application* of sanctions. Even Article 22.8 does not contain any indication regarding the fate of the DSB authorization once the conditions under Article 22.8 are fulfilled.

19. Finally, even if a DSB authorization could be terminated, positive consensus would apply, Article 2.4 of the DSU. Thus, any attempt would have been unlikely to work and certainly would not have worked in the current circumstances. Since the United States and Canada determinated that the EC compliance measure was WTO-inconsistent both WTO members would have blocked any positive consensus in the DSB.

Q2. Does the European Communities agree that, under the DSU as it currently stands, there is no restriction on any party to initiate Article 21.5 proceedings? if not, could the EC elaborate on the legal, procedural or technical reasons which make it impossible or ineffective for a given party to a dispute to have recourse to Article 21.5 of the DSU?

20. Article 21.5 of the DSU does not itself mention who is to initiate the compliance review. However, Article 21.5 expressly refers to the DSU procedures ("these dispute settlement procedures"), which includes, *inter alia*, Article 6, i.e. the legal basis for the DSB to establish panels

[6] The European Communities would refer in particular to the case *Brazil – Aircraft*, WT/DS46, where the DSB authorized the suspension of concessions. This authorization was not revoked despite the fact that the DSB adopted the second Article 21.5 compliance Panel Report and which found the Brazil' compliance measure as WTO consistent.

on the basis of a complaint. Thus, as pointed out under Question 1 it is clear from the context, the object and purpose of the DSU and subsequent practice by WTO Members that it is for a complaining Member to challenge the WTO-consistency of a compliance measure by initiating the proceedings under Article 21.5 of the DSU. Moreover, in our reply to Question 1 the European Communities has also explained why a recourse to Article 21.5 by an original responding party would be ineffective.[7]

Q3. Could the European Communities comment on the "endless loop of litigation" argument made by the United States in paragraph 9 of its first written submission?

21. In paragraph 9 of the US First Written Submission, the United States argues that the EC interpretation of Article 21.5 of the DSU an implementing Member can create an "endless loop of litigation".

22. The European Communities considers that such a scenario is misplaced. In fact, an "endless loop of litigation" due to a "mere declaration of compliance" presupposes that a complying Member adopts a sort of "sham measure" which consequently would be found inconsistent in an Article 21.5 proceeding. The complying Member would consequently enact a second "sham measure" which would then again be found to be WTO-inconsistent under an Article 21.5 proceeding. According to the United States this could go on forever.

23. One does not need a lot of imagination to realize that this scenario is pure science fiction. Indeed, it is based on the very hypothesis that a complying Member would constantly act in bad faith. Such an assumption is certainly not reflected in any past WTO experience. But in addition, the US' argument turns on its head the fundamental principle in the WTO that WTO Members should not be presumed to act in bad faith. Yet, WTO-Members should not be assumed lightly to take a risk of losing their credibility by making in bad faith "mere declarations of compliance". Indeed, under the same logic one could argue that the US' refusal to initiate an Article 21.5 proceeding would create an "endless loop of sanctions".

24. Moreover, as the European Communities has highlighted in its Closing Statement of the First Substantive meeting, Members do not engage in dispute settlement proceedings in order to lose them needlessly and ignominiously.

25. That said, the scenario described by the United States is also completely irrelevant in the present case. While the United States and Canada disagree with the EC compliance measure they have also clearly stated that they do not contest that the European Communities has acted in good faith. Thus, the very basis for the US' theory of an endless loop of litigation does not apply in the present circumstances.

Q4. In its first written submission, the European Communities claims that it should benefit from a presumption of good faith compliance. Canada and the United States have argued against such a presumption and have further argued that the EC compliance measure is in breach of Articles 3.3, 5.1 and 5.7 of the *SPS agreement.*

(a) Could the European Communities comment on the US statement in footnote 124 of the first US written submission?

26. In footnote 124 of its First Written Submission the United States is confused about the use of the terms "principle of good faith" and "presumption of good faith". Furthermore, the United States tries to limit the scope of the principle of good faith to the issue of "burden of proof".

[7] *See* also EC reply to Question 62 regarding the burden of proof under a self-initiated Article 21.5 proceeding.

27. In respect to the relationship between the "principle of good faith" and the "presumption of good faith" the European Communities would refer to its reply in Question 61.

28. As far as the issue of burden of proof is concerned, the European Communities considers that the US' view does not encompass the full scope of the principle of good faith. Indeed, this general principle is well recognized under public international law and the WTO Agreement.

29. The DSU refers in several instances to the principle of good faith, for instance in Articles 3.10 or 4.3 of the DSU. These provisions are unrelated to the issue of "burden of proof".

30. Moreover, the Appellate Body at several occasions expressed the broad nature of the principle of good faith under the WTO Agreement. In *United States – Hot Rolled Steel* from Japan the Appellate Body found

> We see this provision [under the Anti-Dumping Agreement] as another detailed expression of the principle of good faith, which is, at once a general principle of law and a principal of general international law, that informs the provisions of the *Anti-Dumping Agreement*, as well as the other covered agreements.[8]

31. Furthermore, in the case *United States – CDSOA (Byrd Amendment)* the Appellate Body decided that

> The performance of treaties is also governed by good faith.[9]

32. The European Communities would quote from the dispute *European Communities – Sugar*. In this case, the Appellate Body found that

> [The principle of good faith] covers, in our view, the entire spectrum of dispute settlement, from the point of initiation of a case through implementation.[10]

33. Finally, the European Communities would recall the Appellate Body decision in *European Communities – Sardines*:

> "We must assume that Members of the WTO will abide by their treaty obligations in good faith, as required by the principle of *pacta sunt servanda* articulated in Article 26 of the *Vienna Convention.* And, always in dispute settlement, every Member of the WTO must assume the good faith of every other Member."[11] (Footnote omitted)

34. All these cases were unrelated to the issue of "burden of proof".

35. Against this background the European Communities considers that the US' approach to limit the scope of the principle of good faith to the issue of burden of proof falls far short of its actual meaning under the DSU, public international law and the jurisprudence of the Appellate Body or other relevant international bodies.

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[8] Appellate Body Report, *United States – Hot Rolled Steel from Japan*, para. 101.
[9] Appellate Body Report, *United States – Offset Act (Byrd Amendment)*, para. 296.
[10] Appellate Body Report, *European Communities – Export Subsidies on Sugar*, para. 312.
[11] Appellate Body Report, *European Communities – Trade Description of Sardines*, para. 278. Article 26 of the Vienna Convention reads as follows: "Every treaty in force is binding upon the parties to it and must be performed by them in good faith".

(b) Does the European Communities consider that the presumption of good faith compliance it invokes is irrebutable? if not, does it agree that Canada and the United States could submit arguments to rebut that presumption and that it may in return have to provide evidence to support its claim that its compliance measure is compatible with the SPS agreement?

36. The presumption of good faith is rebuttable. However, such a rebuttal can only take place in the appropriate forum. In the present case, this means that the United States and Canada must challenge the EC measure under an Article 21.5 proceeding if they seek a determination that the EC compliance measure is WTO-inconsistent. Conversely, the United States and Canada cannot rebut the presumption of good faith in the present systematic proceedings under Article 22.8 in conjunction with Article 23.1 of the DSU.

37. As already explained, this dispute is about procedural and systemic issues under the DSU. More specifically, this case is about the US' and Canada's unilateral determination that the EC compliance measure is inconsistent, and based on this determination the US' and Canada's continued suspension of concessions and related obligations.

38. This violation by the United States and Canada is independent of the EC compliance measure. Even if the United States and Canada were able to rebut the presumption of good faith compliance, *quod non*, they would still be in violation of Articles 23, 21.5 and 22.8 of the DSU. This is so because they would still have made a unilateral determination of non-compliance and continued to apply sanctions contrary to relevant DSU provisions at the time of the establishment of the Panel. Conversely, the United States and Canada cannot mend this procedural and systematic failure to respect the dispute settlement rules by arguing now about the EC compliance measure.

39. In its Oral Statement the European Communities has asked a simple question which elucidates this point further: Can the United States and Canada contest that the inconsistency of the measure has been removed (Article 22.8) without violating Article 23 if they do not have recourse to WTO dispute settlement[12]? The simple answer is no. Indeed, by contesting that the inconsistency of the measure has not been removed, the United States and Canada are determining unilaterally that the EC measure is WTO-inconsistent. And since they apply sanctions on that basis they are in violation of Articles 23.1, 23.2(a), 21.5 and 22.8 of the DSU. Thus, whether or not the EC measure is *later* to be found WTO-consistent under the proper proceeding has no effect on the *current* violations by the United States and Canada.

(c) Could the European Communities explain whether the responding parties are entitled to the same presumption of good faith application of the retaliatory measures? If not, why?

40. The United States and Canada can also rely on the presumption of good faith for the application of sanctions. However, the principle of good faith requires the United Sates and Canada to apply the DSU in good faith and therefore to initiate Article 21.5 proceedings against the European Communities within a reasonable period of time if they disagree with the EC's view that it is now in compliance. Yet, the United States and Canada have not done this and they even refuse to consider bringing an Article 21.5 proceeding.

41. By bringing this case against the United States and Canada the European Communities has rebutted the presumption that the United States' and Canada's measures are adopted in good faith.

[12] EC Oral Statement, para. 57.

Indeed, the European Communities made a *prima facie* case on why the application of the sanctions by the United States and Canada is in violation of the DSU.

42. The European Communities would note that this situation is normal for every other WTO proceedings. A complaining Member challenging a measure of another Member has to present a *prima facie* case in order to rebut the presumption of good faith. Conversely, until the DSB makes a finding of WTO-inconsistency no Member can be considered to be in violation of its WTO obligations. Thus, every WTO Member enjoys the presumption of good faith or, in other words, the benefit of the doubts.

43. Yet, the problem in the present case is precisely that the United States and Canada are refusing to bring a dispute settlement case to complain against the EC compliance measure. Thus, due to this refusal they cannot rebut the presumption of good faith compliance in the current proceedings, which the European Communities has brought against the United States' and Canadian measures.

Q5. Could the European Communities specify whether it maintains its claim under Article 23.2(c), or whether it limits its claims under Article 23 to violations of Article 23.1 and 23.2(a)? Likewise, does the European Communities consider that it has "provided a solution to the nullification or impairment of benefits" to the United States (see US first written submission, para. 105)?

44. The European Communities does not maintain its claim under Article 23.2(c) because it does not add anything to the violation claims that are pursued.

45. The European Communities has "provided a solution to the nullification or impairment of benefits" to the United States. By removing the inconsistency of the old measure, the European Communities has removed any nullification or impairment of benefits to the United States that previously resulted from a violation (see Article 11.1 of the *SPS Agreement* and Article XXIII:1(a) of the GATT 1994).

46. Contrary to what the United States obviously believes, the United States has no right to see the import ban lifted. It has only a right to see that the EC measure fulfils the conditions set out under the *SPS Agreement*. Since the adoption of Directive 2003/74/EC this is the case. Consequently, the United States (and Canada) currently does not suffer any nullification or impairment as a result of a violation. All the more it is therefore illegal to continue to apply sanctions as if the US' and Canada's benefits were still being nullified or impaired, and as if, therefore, the United States and Canada were "rebalancing rights and obligations". Indeed, what we currently see is that two WTO Members assume an *additional* right under the DSU to apply sanctions against another WTO Member merely on the basis of a unilateral determination of non-compliance.

Q6. The United States argues in paragraph 200 of its first written submission that there is no basis for concluding that Article 21.5 of the DSU imposes on the original complaining Members a greater burden than on the Member already found to breach its WTO obligations and which has failed to implement the DSB recommendations and rulings by the conclusion of the reasonable period of time. Could the EC comment on this argument?

47. The European Communities can only speculate about what the United States has in mind when it pretends that the EC approach would impose under an Article 21.5 proceeding "a greater burden" on the original complaining Member than on the complying Member. The European Communities does not ask for more than what is the logic under Article 21.5 and what has been the constant practice by WTO Members (see our reply to question 1). If the United States considers this ordinary approach as a "greater burden" for the original complaining party so be it. The European

Communities has readily accepted such a "greater burden" for instance in the latest Article 21.5 proceedings concerning *FSC*. Similarly, any other WTO Member, including by the way the United States, has assumed such a "greater burden" in other proceedings. The burden is merely that of a complainant who challenges the WTO-compatibility of measures of other Members.

48. Furthermore, the European Communities would also recall that in the current circumstances the obligation to initiate an Article 21.5 proceeding results from Article 23.1, 23.2(a) of the DSU. Thus, if the United States were not presently applying sanctions as if nothing had happened, the European Communities would not ask this Panel to put the "burden" to initiate a compliance case on the United States.

49. That said, the European Communities would strongly object to the link the United States tries to establish between an Article 21.5 proceeding and the question on whether or not a WTO Member was able to implement the DSB recommendations and rulings within the reasonable period of time. Indeed, these are two completely different issues. Article 21.5 applies to "measures taken to comply". This provision does not make any reference to whether the measure was taken within or outside the reasonable period of time.

Q7. With regard to the European Communities claim of presumption of good faith compliance, how would the European Communities avoid the risk of not distinguishing between meritorious and purely illusory measures purportedly taken to comply as mentioned by Canada in paragraph 62 of its first written submission?

50. The European Communities has already addressed this issue under Question 3. As said above, WTO Members should not be presumed to adopt in bad faith meritorious and purely illusory measures.

51. Moreover, in the present case, all parties and third parties agree that the EC compliance measure is neither meritorious nor purely illusory. Therefore, even though this question may be of certain academic interest it is not necessary to answer to this question in order to resolve the present dispute.

Q8. If the Panel were to address the EC's alternative claim of violation of Article 22.8 of the DSU, do you think it may rely on the presumption of good faith compliance to consider *how* the burden of proof is to be discharged by each party in its examination of the Article 22.8 claim?

52. Yes. The presumption of good faith also applies to the question on how the burden of proof is to be discharged. Since the United States and Canada are contesting the removal of the inconsistency of the measure, they would have to make a *prima facie* case on the WTO-inconsistency of the EC compliance measure. This is the normal procedural rule in WTO proceedings where it is for a Member which contests the WTO-consistency of another Member's measure to bear the burden of proof.

53. The European Communities would add that it has, in its conditional claims, not only invoked Article 22.8 of the DSU, but also Article I:1 and II:1 of the GATT 1994, for which the *prima facie* case of a violation cannot be denied by the United States and Canada. The consequence is that the United States and Canada must invoke a defence and establish and prove that all conditions of that defence are satisfied. Because of Article 22.8, these conditions notably include that there is an ongoing violation of WTO law by the European Communities.

Q9. Could the European Communities comment on the statement of the United States in paragraphs 97-98 of the first US written submission? In particular, could the European

Communities explain why, in the *US – FSC* case, it apparently did not suspend or terminate its suspension of concessions retroactively on 24 November 2004?

54. On 24 November 2004, the United States announced in the DSB that the President had signed into law the American Jobs Creation Act of 2004. At this occasion the US' representative declared that "the repeal of the ETI provision was effective for transactions occurring after 31 December 2004."[13]

55. Thus, on 24 November 2004 the United States declared in the DSB that its compliance measure would only be effective as from 1 January 2005. Conversely, the United States did not argue that it was in compliance as from 24 November 2004. Therefore, the European Communities suspended the application of the sanctions against the United States as from 1 January 2005, the date when the US' compliance measure came into effect.

Q10. Could the European Communities comment on the statement of Canada in paragraphs 40-41 and 61 of Canada's first written submission?

56. In paragraph 40 Canada submits that the European Communities is under an ongoing obligation to comply subject to the surveillance by the DSB. In paragraph 41, Canada argues that its sanctions are due to the DSB authorization by definition WTO-consistent. In order to ensure the security and predictability of the DSU only the DSB can terminate the authorization. Finally, in paragraph 61, Canada maintains that the European Communities could enjoy the presumption of compliance before the adoption of the DSB authorization. Yet, this presumption yields to the DSB authorization.

57. As to the first point, the European Communities does not agree that it is still under an ongoing obligation to comply since the European Communities has already complied. Of course, the European Communities understands that Canada is in disagreement on this point but Canada should then have launched an Article 21.5 proceeding. The failure to do so amounts in the present circumstances to a unilateral determination of non-compliance which is inconsistent with Articles 23.1, 23.2(a) and Article 21.5 of the DSU.

58. Regarding the second point, the European Communities has explained in detail that the DSB authorization does not make the application of sanctions "by definition" WTO-consistent: Article 22.8 of the DSU clearly provides that the application of sanctions is conditional upon, *inter alia*, the continued existence of inconsistency. Once the inconsistency has been removed the application of sanctions shall be terminated. This obligation is self-executing. That is, it must be applied spontaneously and does not require any further determination by the DSB.[14] In this respect, the European Communities has also submitted that the DSB authorization cannot be seen in an isolated way. Rather, the DSB authorization needs to be put into its proper context, in particular it cannot be possible to allow the application the DSB authorization irrespective whether the underlying reason, i.e. the WTO-inconsistency of the old measure, still exists.[15]

59. Furthermore, if Canada's (and the US') approach were correct a panel could never find a violation of Article 22.8 precisely because the defending parties claim that the application of the sanctions is "by definition" WTO-consistent. A panel could never come to a recommendation that the sanctions should not be applied any longer, if at the same time the DSB authorization would make the application of the sanctions "by definition" WTO-consistent. The only way for a panel to overcome this barrier and to reach a recommendation that sanctions should not be applied any longer would be

[13] WT/DSB/M/178.
[14] EC First Written Submission (WT/DS321), para. 93. EC Oral Statement, para. 118.
[15] EC First Written Submission (WT/DS321), paras. 104 *et seq.*; EC Oral Statement, paras. 110 *et seq.*

therefore to conclude that the DSB authorization cannot justify "by definition" the application of sanctions.

60. The European Communities would note that the United States and Canada are rather illogical on this point: On the one hand, when it comes to the violation claim under Article 21.5, 23.1, the defending parties have argued during the First Substantive meeting that the European Communities could bring an Article 22.8 case in order to get the sanctions lifted. On the other hand, when it comes to the violation claim under Articles 22.8 (23.1) the defending parties argue that there can not be any violation because of the DSB authorization. However, if the latter were true, the former would not work.

61. The inherent flaws of the US' and Canada's logic come from the fact that they do not properly distinguish between the existence of the DSB authorization and the application of the sanctions. As explained above, the DSU does not provide for any mechanism for the formal revocation of the DSB authorization. It does, however, provide for a self-executing provision on the application of the suspension of obligations pursuant to a DSB authorization. And this application is not "by definition" WTO-consistent but subject to certain conditions, i.e. the continued inconsistency of the measure.

62. Finally, in respect to para. 61 of Canada's First Written Submission the European Communities has also already explained that the presumption of compliance is in no way affected by the existence of a DSB authorization.[16]

Q11. Could the European Communities comment on the statement of the United States in paragraph 187 of the first US written submission?

63. In paragraph 187 of the US First Written Submission, the United States argues that the European Communities' interpretation of Article 23.2(a) would force a complaining Member into a breach of this provision if it does not immediately agree with the measure or launch an Article 21.5 proceeding.

64. The European Communities replied to this argument in paras. 47 and 48 of its Oral Statement. In fact, the United States seems to get carried away by referring to an alleged need to make an "immediate" determination regarding the WTO-consistency of a compliance measure. Yet, this is not the case before us. Almost two years have passed since the European Communities has adopted its measure in October 2003. Moreover, this measure did not come out of the blue. In November 2000, the European Communities had already notified the legislative proposal to the WTO SPS Committee.[17] Thus, until today the United States and Canada had almost five years to make up their mind on the WTO-consistency of the (proposed) measure. And still they pretend not to have made any determination to this effect and to be unable to do so. Moreover, the United States even denies that there is a "disagreement" with the European Communities on the consistency of the measure within the meaning of Article 21.5.[18]

65. What the United States conveniently overlooks is the fact that since all that time it applies sanctions against EC products. This is indeed a special situation. If the United States were not applying sanctions the European Communities would certainly not be concerned about whether the

[16] EC First Written Submission (WT/DS321), paras. 104 *et seq.*

[17] G/SPS/N/EEC/102 and G/SPS/N/EEC/102 Rev. 1.

[18] Surprisingly, this does not prevent the United States to argue that the European Communities could have brought an Article 21.5 case. But if it were true that there is no disagreement between the United States and the European Communities on what basis could the European Communities then have initiated an Article 21.5 proceeding?

United States needs another five years to come to a conclusion about the WTO-consistency of the EC compliance measure.

66. A retaliating Member has at a minimum a good faith obligation to assess within a reasonable delay the compliance measure. And if it is unable to do so it should suspend the sanctions. If this had been the case the European Communities would certainly not have initiated these proceedings. But the sluggishness of a retaliating Member cannot be at the expense of an implementing Member that has made every effort to comply with its obligations.

Q12. Could the European Communities comment on the US interpretation of "these dispute settlement proceedings" in Article 21.5 of the DSU (see first US written submission, paras. 193 and 199-201)?

67. The European Communities has a different understanding of Article 21.5. In its view Article 21.5 provides for a proper compliance proceeding. The term "these dispute settlement proceedings" encompass the normal rules that apply for dispute settlement proceedings in general such as for instance Article 4 or 6.[19]

68. That said, the European Communities does not disagree that the DSU also provides for other proceedings other than Article 21.5. This could be, for instance, Article 25. However, as explained in response to Question 50, the United States and Canada refused the European Communities' offer to resolve this dispute through an agreed procedure, including recourse to arbitration under Article 25 DSU.

Q13. Having regard to the first claim of the EC, does the European Communities consider that there could be a breach of Articles 21.5 and 23.2(a) of the DSU by Canada and the United States even if the presumed compliance has not actually translated into actual compliance?

69. Yes, as already indicated in our reply to question 4(b), the procedural violations committed by the United States and Canada are independent of whether or not the European Communities has actually complied. The European Communities claims that the United States and Canada are violating Article 21.5 in conjunction with Articles 23.1 and 23.2(a) because they have made a unilateral determination of non-compliance and because they continue to apply sanctions on that basis. Since the United States and Canada have already made such an illegal unilateral determination it does not matter whether the EC compliance measure is WTO-consistent or not. It suffices to state that the United States and Canada have made a unilateral determination they were not allowed to make under the DSU.

70. The European Communities of course understands the defending parties' strategy to distract the Panel from this procedural violation of the DSU by discussing the substantive compliance by the EC measure. However, this discussion cannot mend the violation that has already occurred. Indeed, it would be ironic if the United States and Canada were allowed to justify their illegal unilateral determination of non-compliance under Article 21.5 in conjunction with Article 23.2(a) if they could use these proceedings to discuss the substance of the EC compliance measure. As the European Communities has repeatedly made clear, the present proceedings are not the appropriate forum for such a discussion.

[19] That said, Article 21.5 is not an ordinary panel procedure in that the terms of reference are defined as consisting of the existence or WTO-consistency of the measure taken to comply and in relation to the recommendations which Article 21.5 panels (do not) make.

Q14. Could the European Communities comment on the US statement and its reference to the Appellate Body Report in *US – Certain EC Products* (first US written submission, para. 207 and related footnote)?

71. In paragraph 207 of the US' First Written Submission the United States refers to the Appellate Body statement whereby Article 3.7 of the DSU does not contain an explicit obligation not to apply sanctions without prior authorization. The United States interprets this sentence so as to mean that Article 3.7 does not contain any obligation at all.

72. The United States obviously misinterprets the Appellate Body statement. There is a difference between the Appellate Body statement whereby Article 3.7 does not set out an *explicit* obligation, on the one hand, and the US' interpretation that Article 3.7 does not contain an obligation at all. Rightly so, the United States also quotes the last sentence of the Appellate Body statement in paragraph 120 which reads as follows:

> We consider, however, that if a Member has acted in breach of Article 22.6 and 23.2(c) of the DSU, that member has also, in view of the nature and content of Article 3.7, last sentence, necessarily acted contrary to the latter provision.[20]

73. In the present case, the European Communities applied this Appellate Body' interpretation of Article 3.7. Indeed, if a WTO-Member can act "contrary to Article 3.7" it is clear that this provision also contains a specific obligation.

Q15. Can the presumption of good faith implementation/consistency of the compliance measure override the DSU authorization for suspension of obligations? Please elaborate.

74. The European Communities has difficulties to understand what the Panel means by the word "override" and this word seems rather inappropriate. The European Communities bases its claim, *inter alia*, on Article 22.8 which provides that under certain conditions sanctions may not be "applied" any more. It is true that within the Articles 22.8, 23 claim the European Communities relies on the presumption of good faith. But as explained in our reply to question 4(b) the defending parties cannot escape this presumption in the absence of any challenge of their own under Article 21.5 of the DSU.

75. On the other hand, if the Panel's question implies whether the presumption of good faith terminates the DSB authorization the European Communities would recall that it has never argued this.

Q16. Could the European Communities identify: (i) the document(s) that encompass the risk assessment for the ban on imports of beef from cattle treated with oestradiol 17β for growth promotion purpose, and (ii) the information that served as basis for the provisional measure on imports of beef from cattle treated with the other five hormones for growth promotion purpose? Could the EC also indicate whether this information is publicly available? If yes, since when? If not, has it been made available to the United States and Canada at any point of time?

76. In answering this question, the European Communities refers to the assessment of risk performed by the relevant scientific committee which the applicable Community law defined as the committee competent to perform the risk assessment for this kind of substances in the EC legal system. This is the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) (see 1st EC Written Submission, para. 143). This is also explained in the recitals of Directive 2003/74. Although the Panel's question does not clarify what it means by "risk assessment", the European

[20] Appellate Body Report, *US – Certain EC Products*, para. 120.

Communities uses here the term "risk assessment" to refer to a risk assessment in a strict (narrow) sense.[21] But as the Panel knows, the Appellate Body in the *Hormones* case has clarified that the term "risk assessment" in the *SPS Agreement* is wider in scope because it covers also evidence, considerations, objectives and factors that are also taken into account at the "risk management" phase.[22] The European Communities will indicate separately the basis of its "risk management" that led to the adoption of the new Directive 2003/74.

77. The main documents and information that encompass the risk assessment for the restriction on imports of beef from cattle treated with oestradiol 17β for growth promotion purposes as well as for the provisional restriction of imports of beef from cattle treated with the other five hormones for growth promotion purposes, are the three opinions of the SCVPH of 30 April 1999, of 2 May 2000, and of 10 April 2002.[23] These three scientific opinions explain in detail the scientific information, data and other evidence upon which they are based, and each one of them provides at the end a list of references. In particular, they explain the procedures that were followed and also provide in detail the data and evidence resulting from the 17 specific scientific studies that were initiated by the Commission to obtain as much as possible of the missing scientific information that was identified by the WTO Panel and Appellate Body reports in the *Hormones* case.

78. It should also be clarified that these three scientific opinions of the SCVPH took into account and analysed the scientific evidence and data from any relevant source available at the time, including the opinions from the 1999 United Kingdom's Veterinary Products Committee, the 1999 Committee on Veterinary Medicinal Products of the European Community (CMVP),[24] and the 1999 and 2000 re-evaluations from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) of some of these hormones.

79. The three SCVPH opinions (as well as the other opinions on which they are based) are all public. They were made available to all concerned a few days after their adoption, and were also put on the internet site of the European Commission soon thereafter. Moreover, the results of the 17 scientific studies, after being peer reviewed, led to a number of publications in international scientific journal and reviews and were presented also at international scientific conferences.[25] This is explained in more detail below.

80. The three scientific opinions of the SCVPH were published as follows:

– Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health: Assessment of potential risks to human health from hormone residues in bovine meat and meat products (of 30 April 1999), is on the European Commission's website since April 1999 at:

[21] That is as it is defined in the Codex Alimentarius Commission Procedural Manual, 14th ed., pages 46-47, available at http://www.codexalimentarius.net/web/procedural_manual.jsp.

[22] *See* Appellate Body Report in *EC – Hormones*, at paras. 181 and 206.

[23] They have already been provided to the Panel by both the USA and Canada. *See*: USA list of exhibits nos 4, 17 and 1, respectively; and Canada's list of exhibits nos 2, 4, and 7, respectively. For this reason, the European communities will not submit them again to the Panel.

[24] It should be clarified that both the USA and Canada misinterpret in their first written submission the role of the CVMP and the relevance of its opinion in the Community legal system. The European Communities will explain in greater detail with its rebuttal this important misunderstanding by the defending parties and the erroneous arguments this has lead them to advance.

[25] *See*, e.g., Andersson, Grigor, Rajpert-De Meyts, Leffers and Skakkebaek (eds.): Hormones and Endocrine Disrupters in Food and Water - Possible Impact on Human Health, published by Munksgaard, Copenhagen, 2001 (ISBN 87-16-16462-8). This book contains 43 peer-reviewed papers and discussions from an international workshop held at the University Hospital Rigshospitalet, Copenhagen, Denmark, May 27-30, 2000.

http://web.archive.org/web/20000417013041/europa.eu.int/comm/dg24/health/sc/scv/out21_en.html.

– Review of specific documents relating to the SCVPH opinion of 30 April 1999 on the potential risks to human health from hormone residues in bovine meat and meat products (adopted on 03 May 2000), is on the website since August 2000 at:

http://web.archive.org/web/*/http://europa.eu.int/comm/food/fs/sc/scv/out33_en.pdf

– Opinion on review of previous SCVPH opinions of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products (adopted on 10 April 2002), is on the website since August 2002 at:

http://web.archive.org/web/*/http://europa.eu.int/comm/food/fs/sc/scv/out50_en.pdf.

81. These three scientific opinions of the SCVPH were made available to every person concerned, including of course the USA and Canada. In particular, both the USA and Canada do not deny that they have received these there scientific opinions in time. The USA only claimed, for the first time during the oral hearing on 13 September 2005, that it has not received the details of the 17 studies initiated by the European Commission. Canada has never made such a claim. It should be noted that Canada, Australia and the United Kingdom have made a review of these three opinions of the SCVPH and of the results of the 17 studies mentioned above, and issued their own reviews of these studies. The reviews of these three countries are also publicly available (and actually provided to the panel with the parties submissions).[26] This means that these three countries have had no problem whatsoever to obtain access to all relevant documentation pertaining to the European Communities' risk assessment.

82. The European Communities will also explain in more detail with its rebuttal that the defending members not only received the three scientific opinions but that the European Communities has been in contact with their competent authorities and scientists several times, where the results of the risk assessment have been explained and discussed.

83. As already indicated above, the European Communities took also into account the evidence relating to the factors mentioned in Article 5.2 and 5.3 of the *SPS Agreement*. This is in accordance with the Appellate body findings in paragraphs 205-208 of the Appellate Body report in the hormones case. They are documented in particular in the 1999[27] and 2002[28] opinions of the SCVPH, where specific references to the scientific evidence upon which they are based are explained. These factors and other considerations and the evidence upon which they are based are also explained in recitals 10-

[26] *See* the 1st written submission of the USA, list of exhibits, nos 12 and 16. *See* also 1st written submission of Canada, list of exhibits, no 6. Moreover, the following is an excerpt from the web-site of Health Canada: "How is Health Canada addressing results of the EU commissioned studies on hormonal growth promoters? It is imperative that any decisions taken by the Government of Canada regarding the use of hormonal growth promoters be based on the most accurate interpretation of scientific evidence available. To this end, Health Canada's Veterinary Drugs Directorate (VDD) undertook an intensive review of seventeen studies commissioned by the EU to assess scientific information on the toxicity and safety of hormone-treated beef. VDD's scientific review of the EU studies concluded that residues in meat from animals treated with hormonal growth promoters (when administered according to good veterinary practices) pose **no undue** risk to human health." (Emphasis added). Available at http://www.hc-sc.gc.ca/dhp-mps/vet/faq/growth_hormones_promoters_ croissance_hormonaux_stimulateurs_e.html. (visited on 1 October 2005).

[27] *See* section 3 of the 1999 SCVPH opinion.

[28] *See* section 4.1.4, section 6 and Annex 1 of the 2002 SCVPH opinion.

12 of the new Directive 2003/74. The European communities will provide more details of the evidence and the data upon which its "risk management" phase was based with its rebuttal in this case.

84. The European Communities provides as an exhibit to this submission the results of all the 17 studies initiated by the European Commission and the numerous publications they have given rise to in various peer reviewed scientific journals. When a couple of these studies are not published in peer reviewed scientific journals, a copy of the original of the study is provided.[29]

Q17. Has the European Communities assessed the specific risk associated with residues in meat from cattle treated with hormones for growth promotion purposes according to good veterinary practice? Please provide the risk assessment, as well as the scientific studies on which it relies.

85. Yes, the EC has assessed the specific risk associated with residues in meat from cattle treated with hormones for growth promotion purposes according to good veterinary practice (GVP). As explained above with the reply to question 16, the European Communities' assessed in the specific case of the six hormones the potential adverse effects of the factors mentioned in Articles 5.2. and 5.3. of the *SPS Agreement*.

86. The studies that assessed the specific risk associated with residues in meat from cattle treated with hormones for growth promotion according to GVP are, in particular, the following:[30]

- Study concerning an analysis of 500 samples for the presence of growth promoters, published as "Hormones found in meat samples from regular controls within the EU and from US imports", in Chemical Awareness; issue 9, July 5th, 2000.

- Study concerning an analysis of 500 samples for the presence of growth promoters steroids in meat by gas chromatography coupled to mass spectrometry, published in Journal of Chromatography A, 867: 219-233, 2000.

- Study concerning a survey of anabolic agents in meat, published as "Le contrôle des anabolisants dans la viande", in Annales de Toxicologie Analytique, vol.XII, no.1, 2000.

- Study concerning the long term effects in children to estrogenized meat, published as "Accidental gynecomastia in children", in APMIS 109, suppl. 103: 203-209, 2001.

- Study concerning the use of hormones as growth promoters: genotoxicity and mutagenicity of Zeranol &Trenbolone, published as "Genotoxic potential of xenobiotic growth promoters and their metabolites", in APMIS 109:89-95, 2001.

- Study concerning the metabolic pathways of estrogens as steroidal growth promoting agents, published as "Estrogenic activity of estradiol and its metabolites in the ER-CALUX assay with human T47D breast cells", in APMIS 109: 101-107, 2001.

87. It should also be recalled that one of the critical issues in the assessment of the risk at stake, as identified by the Appellate Body in the hormone case, is to take into account in this specific instance the lack of an harmonised GVP, as well as the conditions of implementation and control of such GVP.

[29] Exhibit EC – 6 (US), Exhibit EC – 4 (CAN).

[30] Copies of the original of these studies as well as their published version, when available, have been provided with the exhibits attached to Question 16.

And as the Appellate Body pointed out, it is possible to deduce that, if a product is said to be safe if GVP is followed, then it **may or may not be safe if GVP is not implemented.** The GVP - or rather *Good Practice in the Use of Veterinary Drugs (GPVD)* as it is called in the Codex Alimentarius Commission (Manual, page 45) - is defined as follows:

> Good Practice in the Use of Veterinary Drugs (GPVD) [ ] is the officially recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

88. The GPVD is, therefore, dependant on what national governments consider appropriate, and is indeed different in each country, as it is dependant on each national authorisation.[31] The definition is, therefore, somewhat circular and hence problematic.[32]

89. The European Communities has evaluated also the specific risks to human, animal and environmental adverse effects associated from the misuse or abuse of these hormones for animal growth promotion purposes. The studies that carried these evaluations are the following:[33]

- The study concerning the application of anabolic agents to food producing animals - health risks through disregard of requirements of good veterinary practice. This multifaceted study has given rise to a number of scientific publication in peer reviewed journals. They are the following:

  1) "Detection of melengestrol acetate residues in plasma and edible tissues of heifers", The Veterinary Quarterly 21: 154-158, 1999.

  2) "Detection of anabolic residues in misplaced implantation sites in cattle", Journal of AOAC International 83(4); 809-819, 2000.

  3) "Suppression of androstenone in entire male pigs by anabolic preparations", Livestock Production Science- 69: 139-144, 2001.

  4) "A sensitive enzyme immunoassay (EIA) for the determination of Melengestrol acetate (MGA) in adipose and muscle tissues", Food Additives and Contaminants 18(4):285-291, 2001.

  5) "Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and to the bovine progestin receptor", APMIS 108: 838-846, 2000.

  6) "Dose-dependent effects of melengestrol acetate (MGA) on plasma levels of estradiol, progesterone and luteinizing hormone in cycling heifers and influences on oestrogen residues in edible tissues", APMIS 108: 847-854, 2000.

[31] For instance, the latest 2005 United Kingdom report on hormones, provided by the USA with its oral statement during the first oral hearing, which is cited very selectively by the USA, states on page 6 that: it is "more likely to have abuses in a context where these hormones are authorised".

[32] For instance, JECFA stated that: "[B]ecause the use pattern of veterinary drugs varies considerably form one country to another and because information on such use generally is not available to JECFA, it is very difficult to estimate the percentage of national herds that are likely to be treated with a substance at any time and consumer consumption patterns from national surveys to a precision that would be sufficient to estimate the intake" (*See* page 7 of the response from the 60th meeting of JECFA to questions raised by the 13th CCRVDF).

[33] Copies of the original of these studies as well as their published version, when available, have been provided with the exhibits attached to Question 16.

7) "Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: Effect of the implant preparations Finaplix-H®, Ralgro®, Synovex-H® and Synovex Plus®", APMIS 109: 53-65, 2001.

8) "Tissue-specific expression pattern of estrogen receptors (ER): Quantification of ER_ and ER_ mRNA with real-time RT-PCR", APMIS 109: 345-355, 2001.

- The study concerning screening water samples for estrogenic &androgenic anabolic chemicals scientist has not yet indicated name of journal and publication date, partly published in APMIS 109, suppl.103: 551-556, 2001.

- The study concerning endocrine disrupting effects of cattle farm effluent on environmental sentinel species, published as "A re-examination of variation associated with environmentally stressed organisms", in Human Reproduction, update vol. 7, no. 3: 265-272, 2001.

90. Moreover, concerning the assessment of the risk associated with residues in meat from cattle treated with hormones for growth promotion purposes and the scientific studies on which it relies, the 1999 SCVPH opinion already refers to this issue, in particular at :

- Discussion on Susceptible populations (page 27)

- Exposure considerations upon misuse (at page 30)

- Exposure in relation to endogenous hormone production in humans at different stages of life (page 34)

- Assessment of excess exposure to oestrogens from consumption of hormone-treated beef (at page 36)

- Assessment of excess exposure to testosterone from consumption of hormone-treated beef (at page 47)

- Assessment of excess exposure to progesterone from consumption of hormone-treated beef (at page 52)

- Assessment of exposure to trenbolone from consumption of hormone-treated beef (at page 57)

- Assessment of exposure to zeranol from consumption of hormone-treated beef (at page 63)

- Assessment of exposure to melengestrol from consumption of hormone-treated beef (at page 67)

- Executive summary (at pages 69 – 73) in particular second paragraph (at page 72).

91. The European Communities reserves the right to develop further with its rebuttal these important issues and it will provide in particular specific evidence from misuse of these hormones that has recently arisen in the territory of the defending Members.

Q18. What is the EC's response to the comments in paragraphs 155 and 156 of the US first written submission on the EC's study of the carcinogenic effect of the oestradiol – 17β to human health? Does the European Communities agree that what is relevant is the risk resulting from human consumption of meat from cattle treated with oestradiol – 17 β for growth promotion purpose according to good veterinary practice?

92. Yes, the European Communities agrees that in principle the risk resulting from human consumption of meat from cattle treated with oestradiol - 17β for growth promotion purposes, according to good veterinary practice, is relevant. But there are a number of very important qualifications.

93. First, this kind of risk, if this was a "real life" situation, then as JECFA has already pointed out in its answer to the CCRDVF, it is very difficult to estimate the GVP and the hormone uses "*to a precision that would be sufficient to estimate the intake*".

94. In reality, however, human beings, including the populations at risks, are exposed to cumulative and synergistic effects, as they may be exposed to multiple sources of hormone and hormone residues, via several intake routes, as well as from endogenous production of some of these hormones. Not only is it extremely difficult or impossible to assess accurately consumer exposure patterns, or other exposures from other environmental or endogenous sources, but it is also virtually impossible to assess all cumulative and synergistic effects that may arise from all potential exposure patterns, including for simultaneous exposure to several of these hormones. Therefore, the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be.

95. Secondly, another important qualification comes from the proper implementation of GVP and the possibilities available to control good veterinary practice, as discussed in the answer to the previous question.

96. In summary, for the European Communities the risk resulting from human consumption of meat from cattle treated with oestradiol - 17β for growth promotion purposes, according to good veterinary practice, is "*assessed in the real world*" where "people live, work and die", or may be suffering from clinical disorders, may be particularly vulnerable segments of the population (e.g. like prepubertal children), etc.

97. More specifically, in paragraphs 155 and 156 of its first written submission the United States claims that the European Communities assessment of the risk in relation to a carcinogenic hazard of oestradiol - 17β is based on studies on the use of oestrogens in contraceptives and hormone replacement studies. This is partly correct. It should be added, however, something the USA does not explain in para. 155 of its 1st written submission, that even JECFA for the first time in its 1999 re-evaluation of oestradiol 17β came to the conclusion that: "*The Committee concluded that oestradiol 17β* ***has genotoxic potential***". As said above, this was the first time JECFA made this finding – compared to its previous 1988 evaluation – and this has *inter alia* led now, again for the first time, to propose the definition of an Acceptable Daily Intake (ADI) for oestradiol 17β, which was not the situation before.

98. Moreover, what the USA also does not explain is that its own responsible health authorities have, for the first time since 2002, declared that oestradiol 17β is proven to be a human carcinogen and it is now listed as such, since 2002, in the USA Annual Report on Carcinogenesis. This latest report for instance states the following:

> "Steroidal estrogens also occur naturally in plants. Currently, more than 360 plants have been identified that have estrogenic activity. A few plants contain the principal estrogens found in mammals, estradiol and estrone (Setchell 1985). Meat and milk also may contain estrogens (Collins and Musey 1985). Veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food producing animals to above their normal levels."[34]

99. On the basis of the most recent evidence from all sources, the USA authorities concluded that "steroidal estrogens are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans, which indicates a causal relationship between exposure to steroidal estrogens and human cancer." For this reason, the 2002 listing of steroidal estrogens as known to be human carcinogens now "supersedes the previous listing of specific estrogens in the Report on Carcinogens (RoC) and applies to all chemicals of this steroid class."

100. Equally, the United States argues against the European Communities assessment of risks by stating inaccurate generalities on the comparison of doses and bioavailability/biological activity, for different mode of intake and uses of the hormone. What is most importantly missing in the United States reasoning is the intrinsic and significant variability of the biological activities of this hormone, and its potential pathological consequences, according to individual sensitivity, stage of development, etc. Furthermore, it claims that "*oestradiol - 17β is* ***generally*** *inactive when given orally*" (emphasis added), while this argument is well known to be still controversial and not consensually accepted by the scientific community. It also claims, in footnote 167, without providing any relevant and peer reviewed scientific evidence to support its claim, how the results of some of the studies cited by the European Communities should be interpreted.

101. Most importantly, carcinogenic activities of molecules can not be assessed with the reasoning and the biological thresholds available to assess their acute or chronic toxicity, as does the United States. This is particularly the case when compounds have genotoxic activity. The carcinogenic activity of biologically active molecules, especially when their normal (as opposed to pathological) activity is related to radical modifications of developmental phenotypes and of cellular growth and development, indeed may often manifest itself at sub chronic level, with low doses under permanent exposure or with delayed potential effect. This carcinogenic activity may only manifest itself after a long period of time and it may even go unnoticed in classical acute, chronic or even sub chronic studies. Finally, as noted by the United States itself, synthetic or naturally occurring molecules bear different hazards, and contrary to the United States claim, results obtained from studies on one or the other are difficult to extrapolate to one another.

102. The European communities will provide more detailed information and specific data on this important issue with its rebuttal in this case.

Q19. Could the European Communities explain why the ban on testosterone, progesterone, MGA, TBA and zeranol is now only provisional?

103. The reason, in summary, is that the most thorough and recent information obtained in the latest assessments of the risk for each of these five hormones has been found to be insufficient, inconclusive and contradictory. Even if the insufficiencies and contradictions amount to different extents for each of the five hormones, they do not permit to reach firm conclusions and to perform a definitive risk assessment. For instance, it is not possible to set acceptable thresholds for these hormones as used in growth promotion or acceptable thresholds for their residues.

[34] Available at http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540.

104. This is explained more specifically and in detail in the assessment of risks performed by the SCVPH, in particular in its opinion of 1999 (see also replies to questions 67 and 73), as well as in the subsequent European Communities' new Directive 2003/74, in particular in its 7th, 10th and 13th recitals, as well as in its operative provisions. Recital 7 explains:

> "As regards the other 5 hormones, the Scientific Committee on Veterinary measures relating to Public Health (SCVPH) assessment is that, in spite of the individual toxicological and epidemiological data available, which were taken into account, the current state of knowledge does not make it possible to give a quantitative estimate of the risk to consumers".

105. Consequently, as explained in the recital 10 of the said Directive:

> "taking into account the results of the risk assessment and all other available pertinent information, it has to be concluded that, in order to achieve the chosen level of protection in the Community from the risks posed, in particular for human health, by the routine use of these hormones for growth promotion and the consumption of residues found in meat derived from animals to which these hormones have been administered for growth promotion, it is necessary to continue provisionally to apply the prohibition to [these] five hormones. Furthermore, [ ] the provisional prohibition of these five hormones should apply while the Community seeks more complete scientific information from any source, which could shed light and clarify the gaps in the present state of knowledge of these substances"

106. Finally, recital 13 concludes:

> "The proposed amendments to Directive 96/22/EC are necessary to achieve the chosen level of health protection from the residues in meat of farm animals treated with these hormones for growth promotion purposes, whilst respecting the general principles of food law set out in Regulation (EC) No 178/2002 and the international obligations of the Community. Moreover, there is no other means that is reasonably available at present, taking into account technical and economic feasibility, which is significantly less restrictive of trade and can achieve equally effectively the chosen level of health protection. [ ] "

107. Furthermore, the operative provisions of the said Directive require that the ban on these 5 hormones be provisional (Article 3.1 of the amended Directive), and Article 9 of Directive 2003/74/EC (article 11a of the amended former Directive) requires that additional information is sought and that the measures applied be kept under regular review, with a view to timely present any necessary amendments.

108. The prohibition on the use of these five hormone for animal growth promotion is *now* provisional, while it was not so in the Directive 96/22/EC, for a number of reasons. First, the new scientific studies that have been initiated since the DSB recommendation in the hormone case, in order to address the scientific information that was found by the panel and the Appellate Body to be missing, have now identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge now available on these hormones, which have together reinforced the need for even more studies. Second, the previous Directive 96/22/EC was drafted in 1995 and adopted in 1996 as a codification of the pre-existing European Community measures in this area. This happened at a time where international guidance on how to perform a risk assessment was not yet available to tackle situations where scientific information was insufficient to conclusively assess a particular risk, in accordance with a member's chosen level of health protection. For example, at that time there did not exist standards nor guidelines from the Codex Alimentarius Commission on how to

perform a risk assessment and risk analysis. Moreover, the provisions of Article 5.7 have now been clarified in a number of panel and Appellate Body reports, starting with their reports in the *hormones* case, which was not the legal situation before 1996.

109. Substantive international discussions have lead to the development of the Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius Commission[35] after 1996. This has only been adopted by the Codex Alimentarius Commission at the 26th Codex Alimentarius Commission meeting at Rome in July 2003. The relevant concepts developed there have been taken into account by the European Communities and have now influenced the drafting of its framework Food Law, namely Regulation 2002/178/EC. In the context of temporary measures, articles 6 and 7 thereof are particularly relevant, and they read :

> Article 6 - Risk analysis
>
> 1. In order to achieve the general objective of a high level of protection of human health and life, food law shall be based on risk analysis except where this is not appropriate to the circumstances or the nature of the measure.
>
> 2. Risk assessment shall be based on the available scientific evidence and undertaken in an independent, objective and transparent manner.
>
> 3. Risk management shall take into account the results of risk assessment, and in particular, the opinions of the Authority referred to in Article 22, other factors legitimate to the matter under consideration and the precautionary principle where the conditions laid down in Article 7(1) are relevant, in order to achieve the general objectives of food law established in Article 5.
>
> Article 7 - Precautionary principle
>
> 1. In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment.
>
> 2. Measures adopted on the basis of paragraph 1 shall be proportionate and no more restrictive of trade than is required to achieve the high level of health protection chosen in the Community, regard being had to technical and economic feasibility and other factors regarded as legitimate in the matter under consideration. The measures shall be reviewed within a reasonable period of time, depending on the nature of the risk to life or health identified and the type of scientific information needed to clarify the scientific uncertainty and to conduct a more comprehensive risk assessment.

Q20. Could the European Communities explain why it has banned oestradiol 17β treatments of animals for growth promotion, and the meat derived from those animals, while allowing its continued use for therapeutic and zootechnical purposes (Canada's first written submission, para. 104)?

110. The European Communities would like to recall that the Appellate Body has reversed the panel's findings on the issue concerning the occasional use of the hormones for therapeutic or

[35] *See* at ftp://ftp.fao.org/codex/Publications/ProcManuals/Manual_14e.pdf

zootechnical purposes.[36] Therefore, arguments of this kind by the defending parties in the context of these proceedings attempt to reintroduce a debate that they have lost at the Appellate Body level. A short reply to this question, therefore, is that this issue is now irrelevant.

111. Nevertheless, the European Communities will provide again some information and reserves the right to further develop its views on this issue in the remaining stages of these proceedings. First, the new Directive 2003/74 does not allow all uses for therapeutic and zootechnical purposes, but only a very few (Article 5a.1 and 5a.2 of the new Directive), for which no viable effective medicinal alternatives exist, and on a defined temporary basis, pending availability of alternative treatment methods, as follows :

Treatments:

– the treatment of foetus maceration or mummification in cattle, or

– the treatment of pyometra in cattle,

Zoo technical:

– oestrus induction in cattle, horses, sheep or goats, until 14 October 2006.

112. Secondly, these treatments must be carried out under strict veterinary oversight, by the veterinarian himself, on farm animals which have been clearly identified and documented, and under strict conditions of control and holding of the hormone (article 5a.3 of the new Directive). This is in striking contrast to the availability of this hormone in the United States and Canada, as an "over the counter product" (OTCs) which are freely available to every lay person.

113. Why were these uses authorised, and how do they meet the chosen level of protection of the European Communities? The difference between the risks from the use of this and the other hormones as growth promoters and of other uses arises from their differential impact on consumer exposure to the hormone, as well as from the different level of oversight of these different uses. Contrary to Canada's view, the European Communities has based its new measure precisely on available risk assessments, in particular the SCVPH opinion which has considered the use of hormones as growth promoters. Here it is used systematically and freely in almost every animal produced, whereas the treatments for therapeutic and zoo technical purposes allowed in the European Communities, are only allowed in few animals and rare occasions, in order to treat particular conditions, and on animals under strict veterinary control.

114. These temporary exemptions, based amongst others on animal health and welfare, are still under consideration. Besides, these therapeutic or zootechnical treatments pose no risk because the animals are intended to be slaughtered in the near future. In practice, therefore, there is a huge difference between the systematic use of growth promoting hormones in animals intended for beef, compared with the occasional use by a veterinarian for treating a sick animal. If at all, the consumer exposure from this kind of use cannot be compared to that resulting from the systematic use of growth promoting hormones in all beef producing cattle. If all hormonal growth promoters are used in the same manner as they are in the United States, 96% of all beef cattle in feedlots are implanted at least once[37], leading to a much higher exposure.

115. The other two treatments allowed by the European Communities are rare occasions. Specialist veterinary practitioners have generally not more than one case per year. It is moreover highly unlikely

[36] *See* Appellate Body Report, *EC – Hormones*, at paras. 221-225.
[37] *See* NAHMS, 2000, cited by Scheffler *et al*., 2003.

that animals treated with these are slaughtered. In must be reiterated that the use for these purposes is supported by the report of the Veterinary Medicinal Products of the European Community (CVMP) in December 1999. It must be stressed that the purpose of the CVMP evaluation was strictly limited to this kind of use only and did not consider the use of the hormones for growth promotion purposes, as both the USA and Canada wrongly argue.

116. Moreover, as laid out in Directive 2003/74, the uses for therapeutic and zootechnical purposes are authorised under conditional and provisional terms, and the reasons for it are explained in Recitals 11 and 12, and in the operative provisions of article 5a of the new Directive. Recital 11 states :

> "However, the use of certain of the above substances, where this is necessary, for therapeutic purposes or zootechnical treatment may continue to be authorised as it is not likely to constitute a hazard for public health owing to the nature and the limited duration of the treatments, the limited quantities administered and the strict conditions laid down in Directive 96/22/EC in order to prevent any possible misuse."

117. Recital 12 states :

> "However, in the light of the existing information it is appropriate to limit as far the exposure to oestradiol 17β and only authorise those treatments for which no viable effective alternatives exist. In general, there are alternative treatments or strategies available to replace most of the uses of oestradiol 17β for therapeutic or zootechnical purposes. Nonetheless, studies appear to show that at present no viable effective alternatives exist in all the Member States for certain treatments which are currently authorised. In order to allow for the necessary adjustments and in particular for the authorisation or the mutual recognition of the pharmaceutical products needed, it is appropriate to phase out the use of oestradiol 17β for oestrus induction over a given period. It is also appropriate to maintain the possibility of authorising, under strict and verifiable conditions so as to prevent any possible misuse and any unacceptable risk for public health, its use for the treatment of certain conditions (foetus maceration or mummification and pyometra in cattle) which have serious consequences for animal health and welfare. It is necessary to review this possibility within a given time."

118. According to the amended Directive, the zootechnical treatment temporarily authorised will be phased out in October 2006. The two other therapeutic treatments authorised will be phased out in relation to the outcome of a report on alternative methods, which is to be presented in October 2005.

Q21. Is there a regulation restricting the residue levels of the relevant six hormones in meat in the EC's health regulations or in any other countries' health regulations? If not, why would such a regulation not be a reasonable alternative to the EC's current definite ban on the use of oestradiol – 17 β for growth promotion purposes and to the provisional ban of the use of the other five hormones for the same purpose? Does the present EC measure eliminate similar risks to human health arising from these hormones when used for other purposes?

119. No, the European Communities' legislation does not lay down maximum residue limits (MRL) or other thresholds of unacceptable residue levels for the relevant six hormones in meat. The Member States of the European Communities do not have their own legislation on these matters because they are pre-empted by Community law.

120. There are several reasons why it is neither a reasonable nor a sustainable alternative to the current Community measure prohibiting permanently oestradiol 17 B and the other five hormones provisionally for growth promotion. First, as cited in our reply to question 17, the JECFA itself

indicates that it is not possible to estimate the hormone intake from meat, which would be a prerequisite for the design of such thresholds. The European Communities' scientists and experts concur with that view, and are of the opinion that one can not set thresholds in this instance. Second, one other important reason why residues limits are not fixed is that these hormones are also produced endogenously both by the animals and humans at different levels which vary considerably, which also impairs the setting of fixed threshold values. Third, different values might have to be set for different populations, according to their varying susceptibility to these hormones and hormone residues, or whether they would be populations at risk or not. It is well established that variable limits of residue levels for different populations would be practically impossible to implement.

121. Accordingly, and with the main objective of limiting the risks imbedded with additive intakes from cumulative and uncontrolled sources, the European Communities has adopted its new implementing measure as it now stands, namely a provisional or definitive ban, depending on the hormone, with a very limited number of highly controlled exceptions, pending further assessment. As a consequence, and for the reasons explained above, thresholds of residues from the banned hormones could not and have not been set.

122. As regards the second part of the question (that is does the present EC measure eliminate similar risks to human health arising from these hormones when used for other purposes), the short answer is yes.

123. The relevant Community legislation allows, where appropriate, to take into account and to provide for measures adapted to the different levels of risks presented by different uses. However, a proper answer to this last part of the question should also clarify that the risks arising from the uses authorised for other purposes, such as therapeutic and zootechnical purposes, are in fact either not present or are not similar, but distinctly lower in magnitude, as explained in detail in our answer to question 20. This is precisely referred to in recital 11 of Directive 2003/74 cited above.[38]

Q22. Does the European Communities agree that JECFA conducted new safety assessments for two of the five hormones (progesterone and testosterone) in 1999 and reaffirmed their safeness when used according to good veterinary practice? JECFA also conducted risk assessments with respect to three hormones since the 1980s and concluded that they are safe within the recommended ADIs. Do the conclusions of JECFA constitute "available pertinent information" that shall be taken into account by the EC in its risk assessment and in the context of Article 5.7 of the *SPS Agreement*? What are the EC's comments to the conclusions of the risk assessments by JECFA? (US first written submission, para. 127)?

124. The European Communities agrees that JECFA has conducted, incidentally without being asked, a new safety assessment on the use of progesterone and testosterone for growth promotion in 1999. The European Communities has asked JECFA to provide it with the underlying scientific evidence that claims to have considered but it never saw the basic information and raw data on which it is based. This information appears to have been provided directly only to JECFA, probably pursuant to exchanges with the industry, but it was not accessible to the European Communities, as was not accessible the detailed safety assessment of the United States and Canada, and in particular the detailed data on which it might have based its assessment. The European communities would welcome any further attempts this Panel may like to undertake in order to obtain this underlying information and make it available to it and the other parties to this dispute.

[38] Moreover, an example is provided by Commission Regulation (EC) No 1873/2003, amending Annex II to Regulation (EEC) No 2377/90, OJ L 275, page 9, 2003, regarding the use of progesterone for therapeutic or zootechnical uses, the recitals of which explain in detail the conditions under which such used is authorised.

125. Do the conclusions of JECFA constitute "available pertinent information" that shall be taken into account by the European Communities in its risk assessment? Yes, the conclusions of JECFA do constitute part of the pertinent information, and they were actually taken into account both by the SCVPH that has issued the three scientific opinions on the same hormone and the same uses, and by the European Communities authorities that have drafted the new Directive 2003/74.

126. To comment more specifically on the conclusions of the JECFA's risk assessments, the European Communities would like to refer first to extracts from its own SCVPH opinions which specifically addressed the JECFA assessment. For example, the 1999 opinion of the SCVPH discussed at several places the re-evaluation made by JECFA, as follows:

- **1999 SCVPH opinion (page 9).** In a three generation study of rats receiving zeranol at levels up to 0.20 ppm throughout gestation, it has been concluded that the fertility of the offspring is not affected (JECFA, 1988). However, male mice exposed *in utero* to zeranol (150 μg/kg of body weight injected on days 9 and 10 of gestation) show testicular abnormalities (regressive changes in the germinal epithelium and Sertoli cells, and immature morphology of Leydig cells) when testes are examined at 45 days of postnatal life (Perez-Martinez et al., 1997). Moreover, in a multi-generational study, it has been shown that trenbolone acetate, administered to female rats at dietary concentrations of 3 and 18 ppb between 2 weeks before mating and 3 weeks delivery, exert effects on reproductive performance which are more marked in F2 pups than in F1 pups of a comparable age. Indeed, female F1 pups from F1-treated parents show signs of virilization, a delay in the mean vaginal opening and the presence of occlusive strands in the vagina or incomplete vaginal opening. Male pups show a delay in the occurrence of testicular descent and a decrease in weights of seminal vesicle, prostate, testes an epididymis. In addition, in F2 pups from both sexes the adrenal weight was also decreased (JECFA, 1988).

- **1999 SCVPH opinion (page 15).** Experiments in rats, mice, hamsters, dogs, pigs, cattle, sheep or monkeys have shown that exogenous sex hormones, including natural steroids as well as growth promoters (such as trenbolone acetate, zeranol or melengestrol acetate), administered by ingestion, injections or implants, induce dosedependent deleterious effects on reproduction in males and females (JECFA, 1988).

- **1999 SCVPH opinion (pages 20, 27/28).** Since the years when preceeding reports were written, such as the FAO/WHO or JECFA monographs knowledge has greatly increased, in particular on oestrogens. Different types of hormonal receptors (α and β) have been identified and their functions better defined. Also, steroid metabolism has been better studied. Genotoxic effects, independent from the presence of hormonal receptors, have been recognized for metabolites of the parent compounds. These concern essentially catechol-oestrogens and corresponding quinones, in particular 4 hydroxylated derivatives (Service, 1998). In addition, activation reactions during oestrogen metabolism contribute by oxidative stress to genotoxic effects. The possibility of synergism between the genotoxic activity of selected oestrogen derivatives and the classical promotional effect of steroïds cannot be excluded. A crucial question is whether consumption of meat from cattle treated with hormones under conditions approved in the USA *vs* non hormone-treated cattle, causes increased exposure to these hormones. The first step in this determination is a calculation of the theoretical increased daily hormone intake when consuming beef from treated as opposed to untreated animals. The recent JECFA report (of February, 1999) presented calculations of a theoretical excess maximum intake (μg/person/day)

of oestrogen (E2 +oestrone [E1]), testosterone and progesterone (see table A3). From this overview, referring to products presently licensed in the USA, it is obvious that, with the exception of pregnant heifers, the use of these growth promoting hormones will result in an additional excess daily intake of oestrogens of 1.1 to 83.9 ng/person (E2 + E1), of progesterone of 64-467 ng/person, and of testosterone of 5-189 ng/person. It is worthwhile to indicate that these data refer to the parent compounds only and do not include contributions from metabolites. It should also be noted that these hormone implant-induced increases in hormone levels result in oestrogen and testosterone exposures below that which would occur upon consumption of beef from pregnant heifers. However, meat from pregnant heifers accounts for only a relatively small amount of the beef consumed, as these animals are slaughtered only incidentally.

- **1999 SCVPH opinion (page 28/29).** The data show that premenopausal women have the highest levels of endogenous oestrogen (oestradiol and estrone) and progesterone. Oestradiol and progesterone production rates in premenopausal women during the follicular phase have been determined to be approximately 445 μg/day and 418 μg/day, respectively (JECFA, 1987). During pregnancy, oestradiol levels rise dramatically to approximate values of 18,000 pg/ml (Goodman, 1996). Oestradiol and progesterone production rates during late pregnancy have been determined to be approximately 13,800 μg/day and 94,000 μg/day, respectively (JECFA, 1987). In men, daily production rates for oestradiol and progesterone are approximately 48 μg/day and 416 μg/day, respectively (JECFA, 1987). In prepubertal boys, oestradiol and progesterone production rates have been reported as being 6 μg/day and 150 μg/day, respectively (JECFA, 1987). Thus, prepubertal and postmenopausal women and prepubertal and adult men have the lowest levels of endogenous oestrogens and progesterone and thus would represent the individuals most likely to be at increased risk for adverse health effects that might be associated with exposure to exogenous sources of oestrogens. As expected, men have the highest levels of blood testosterone and the daily production rate has been determined to be approximately 6,500 μg/day (JECFA, 1987). Testosterone levels are much lower and similar in women and prepubertal men. It has been reported that daily production rates of testosterone are between 140 to 240 μg/day in adult women and 32 and 65 μg/day in prepubescent girls and boys, respectively (JECFA, 1987). These data suggest that all women and prepubertal men represent the individuals at greatest risk for adverse health effects that might be associated with exposure to exogenous sources of testosterone.

- **1999 SCVPH opinion (page 33/34).** 4.1. 17 β-oestradiol. 17β-Oestradiol (E2), estra-1,3,5 (10)-triene-3,17β-diol, is an 18-carbon steroid hormone and the most potent of the naturally occurring oestrogens. This hormone is produced primarily by the developing follicle of the ovary in adult females. E2 exerts its pleotropic biological effects on cell growth and differentiation largely through receptor-mediated mechanisms. E2 binds with high affinity and high specificity to intracellular proteins know as oestrogen receptors (JECFA, 1988; JECFA, 1999; Anstead et a., 1997). Two subtypes of oestrogen receptor (ER) are known, ER-α and ER-β. It is known that these proteins can form both homo- and heterodimer complexes, yet current information about the ER-β subtype is limited. The value of the dissociation constant of E2 for the ER-α is in the 0.1-1.0 nM range (Anstead et al., 1997; Giguere et al., 1998). The aromatic A-ring and 3-OH group of E2 are known to be important components of the ligand binding activity and receptor activation activities of E2.

- **1999 SCVPH opinion (pages 34, 37).** *4.1.2. Oestradiol disposition in the target animal.* After administration of oestradiol benzoate, the major metabolites found in muscle were 17α-oestradiol (38-70% of extracted radioactivity) and E1 (17-45%). The pattern of metabolites in fat was similar to that in muscle. The highest residues were found in kidney and liver. The major oestrogenic metabolites in kidney were 17α-oestradiol, 17α-oestradiol-glucuronide, E2 and E1. In liver, the major metabolite could not be identified (40% of the extracted radioactivity). E2, E1, estriol, and glucuronides accounted for the remaining radioactivity (JECFA, 1988; Dunn et al., 1977). The nature of the unidentified polar metabolites from livers of steers was investigated in another study using radiolabeled E2. The major polar metabolite was the β-Dglucopyranoside of 17α-oestradiol. The 3-β-D-glucuronate of 17α-oestradiol, and other 17-glycosides of oestradiol were also characterized (JECFA, 1988; Rao et al., 1979). Recent studies have begun to consider the formation in cattle of the major oestrogen metabolites found in humans, i.e. the 2-OH, 4-OH and 16α-OH-oestrogens. While it is likely that these routes of metabolism are present in cattle, quantitative measures are not yet published. At its February, 1999 meeting, JECFA established the ADI for 17β-oestradiol as 0-50 ng/kg bw/day. This value is based on a study in postmenopausal women where conjugated equine oestrogens at doses of 0.3, 0.62. 1.2 and 2.5 mg were administered for two weeks followed by no treatment for three weeks. This regimen was repeated four times after which serum levels of corticosteroid binding protein (CBG) were determined. No increase in CBG levels was detected at the 0.3 mg dose (equivalent to 5 μg/kg bw/day) which was thus considered to represent the no-observed-effect level (NOEL). In another analysis (it is not clear if this was part of the same study or a different one), the dose of 0.3 mg of conjugated equine oestrogen was determined to be the NOEL for induction of serum concentrations of follicle-stimulating hormone, angiotensinogen, SHBG and CBG. It was stated that fine-particle 17ß-oestradiol and the conjugated equine oestrogens were equipotent for all four hormone-dependent end points. In a separate study, the bioavailability of fine-particle 17β-oestradiol administered orally was determined to be 5% compared to a dose administered intravenously. Sixty percent of the fineparticle 17β-oestradiol dose was determined to appear in the serum as estrone and estrone sulfate. While the results of these studies would appear to indicate that the maximum excess exposure level (84 ng/person/day) for oestrogen derived from hormone-treated beef is below the NOEL, there are several concerns. First, neither the actual data nor references to peerreviewed publication of this data were available. Second, it is uncertain whether the use of fine-particle 17β-oestradiol, and in particular conjugated equine oestrogens, represents appropriate surrogates for consumption of oestrogens in association with beef. The equine oestrogens consist predominately of equilin and equilenin, which are chemically different from oestradiol. In the USA, the FDA has established an acceptable level of exposure for oestradiol (Table 3). These values represent parent hormone residue levels in uncooked meat that are considered unlikely to produce any physiological effects in individuals chronically ingesting animal tissues.

Table 3: Acceptable levels of oestradiol levels in beef (Ref.: Code of Federal Regulations (CFR) 21, Part 556, Tolerances for residues of new animals drugs in food)

Tissues	Oestradiol (ng/kg)
Muscle	120
Liver	240
Kidney	360
Fat	480

The FDA guidelines state that: "… no physiological effect will occur in individuals chronically ingesting animal tissues that contain an increase of endogenous steroid equal to 1% or less of the amount in micrograms produced by daily synthesis in the segment of the population with the lowest daily production. In the case of oestradiol and progesterone, prepubertal boys synthesize the least, in the case of testosterone, prepubertal girls synthesize the least" (taken from Andersson and Skakkebaek, 1999).

- **1999 SCVPH opinion (page 46).** *4.2.1. Pharmacokinetics and Biotransformation of Testosterone in animals.* Testosterone or testosterone propionate is administered by subcutaneous implantation in the ear. The ear, along with any residual drug, is discarded at slaughter. The dosage of testosterone varies with the manufacturer of the implant, but is most often 200 mg per animal (JECFA, 1988). In the circulatory system of the animal, testosterone derived from the implant is indistinguishable from endogenous testosterone, i.e. enzymatic transformation of the biologically active molecule into less active metabolites. Excretion is predominately via the biliary route, and to a lesser extent via the urine. In general, the fraction of the hormone eliminated in the urine is in the conjugated form, while the fraction found in the feces is in the free form. For testosterone propionate, enzymatic cleavage of the ester produces testosterone which, is again metabolized as the endogenous compound (Hoffmann and Karg, 1976; Hoffmann and Evers, 1986).

- **1999 SCVPH opinion (page 47/48).** At its February 1999 Meeting, the JECFA established for testosterone an ADI of 0.2 ug/kg bw (14 µg/70 kg person) on the basis of a study in eunuchs. This value includes a safety factor of 1000 to protect more sensitive populations and because of the small number of subjects in the study used to determine the NOEL. In that study, oral administration of a dose of 100 mg/day (equivalent to 1.7 mg/*kg* bw/day) of fine-particle testosterone to five eunuchs had no effect on sexual function indexes while a dose of 400 mg/day restored full sexual function. The dose of 100 mg/day was taken as the NOEL in this study. In another study in postmenopausal women, treatment with 10mg/day methyltestosterone was found to induce signs of virilisation. The ADI for testosterone established by the JECFA (14 µg/person) is greater than the highest excess exposure to testosterone (189 ng/person) that could occur from ingesting hormone-treated beef. However, there are concerns regarding the strength of the study that provided the data for determination of the ADI. First, neither the actual data nor reference to a peer-reviewed publication was provided. Second, the dose-response was limited to two doses and the ADI was estimated from just a single dose where no effect was observed, rather than a curve derived from all the data available. The tolerance levels for testosterone levels in uncooked tissues of steers and calves established by the FDA (Ref.: Code of Federal Regulations (CFR) 21, Part 556, Tolerances for residues of new animals drugs in food) are:

Tissue	Testosterone (μg/kg)
Muscle	0.64
Liver	1.3
Kidney	1.9
Fat	2.6

Based on these levels, consumption of 500 g/day of beef (300 g muscle, 100 g liver, 50 g each of kidney and fat) would result in exposure to approximately 0.6 μg/person/day. The maximum excess exposure to testosterone estimated to occur upon consumption of meat from hormone treated cattle, 189 ng/person/day (Table A3, Annex) represents 33% of the acceptable level established by the FDA (0.6 μg/person/day) which also represents approximately 1-2% of the daily production rate for testosterone of 32 μg/day estimated for prepubertal girls. However, there is considerable uncertainty associated with the validity of the daily production rate data. It is possible that this value has been over estimated by one to two orders of magnitude, in which case excess testosterone intake from hormone-treated beef could at best exceed the 1% FDA safety margin and at worst be greater than that naturally present.

- **1999 SCVPH opinion.** *Testosterone Levels in Human Blood.* As expected, men have the highest levels of blood testosterone (Table 1, section 4.1) and the daily production rate has been determined to be approximately 6,500 μg/day (JECFA, 1987). Testosterone levels are much lower and similar in females and prepubertal males. It has been reported that daily production rates of testosterone are between 140 to 240 μg/day in adult women and 32 and 65 μg/day in prepubescent girls and boys, respectively (JECFA, 1987). These data suggest that all females and prepubertal males represent the individuals are greatest risk for adverse health effects that might be associated with exposure to exogenous sources of testosterone.

- **1999 SCVPH opinion (page 51) 4.3. Progesterone.** Progesterone, pregn-4-ene-3, 20-dione, is a C-21 steroid hormone and the most potent endogenous progestogen. This hormone is present in all steroid producing organs, and its production rate varies widely as a function of the phase of a woman's menstrual cycle and pregnancy. The major physiologic function of progesterone is to prepare the uterus for implantation and to maintain pregnancy. The production of progesterone in the corpus luteum of the ovary in adult females is controlled by pituitary luteinizing hormone. Progesterone is essential for uterine development, implantation, blastocyst development and maintenance of the fetus and the uterus during pregnancy. Progesterone opposes some of the effects of oestrogens, and in non-pregnant females, this hormone inhibits the cyclic release of luteinizing hormone and follicle stimulating hormone. The actions of progesterone require prior stimulation with oestrogens, perhaps to increase expression of progesterone receptor (PR). The PR is a member of the steroid hormone superfamily of receptor proteins and mediates the biologic activity of progesterone through gene regulatory mechanisms (Mahesh et al., 1996; Katzenellenbogen, 1996). In animals, progesterone is used primarily in combination with oestrogenic compounds in order to improve their rate of weight gain and feed efficiency, and to suppress oestrus in feedlot heifers.

- **1999 SCVPH opinion (page 51).** Progesterone is administered by subcutaneous implantation in the ear. The ear, along with any residual drug, is discarded at slaughter. The dosage of progesterone is 200 mg per animal (JECFA, 1988). In the circulatory system of the animal, progesterone derived from the implant is

indistinguishable from endogenous progesterone (Baird et al., 1969). The metabolism of progesterone in cattle has been investigated using radiolabeled compound (Estergreen et al., 1977; Purdy et al., 1980; Lin et al., 1978). Animals were administered progesterone, 50μg/kg twice daily for 15 days. Each of the last three injections contained 0.9 mCi [14C]-progesterone and the animals were killed 2-3 hours after the final treatment. Most of the radioactivity in all extracts corresponded to the parent compound (54% of the free radioactivity in muscle and 69 and 73% of the free and conjugated radioactivity, respectively in fat), (Lin et al., 1978). The major metabolites detected in muscle (16% of total radioactivity) included: 5α-pregnane-3, 20-dione (9%); 20-β-hydroxy-4-pregnen-3-one (8%); 3α-hydroxy-5β-pregnan-20-one (13%); and 3α-hydroxy-5α-pregnan-20-one (3%). The major metabolite detected in fat (62% of the total radioactivity) was 20-β-hydroxy-4-pregnen- 3-one (11%), (Estergreen et al., 1977). Little is known about the specific enzymes in cattle that metabolize progesterone, although hepatic cytochrome P450 enzymes are likely involved in the metabolic clearance of this hormone.

- **1999 SCVPH opinion (page 52/53/54).** *4.3.4. Assessment of excess exposure to progesterone from consumption of hormone-treated beef.* Table A3 (Annex) shows that consumption of beef from hormone treated vs non-treated non-pregnant cattle results in exposure to excess levels of progesterone ranging from 64 to 467 ng/person/day, depending upon the implant used. At its February 1999 Meeting, the JECFA established for progesterone an ADI of 0-30 μg/kg bw (0-2,100 μg/70 kg person). This value was based on studies where a lowest-observed-effect level (LOEL) of 200 mg fine-particle progesterone (equivalent to 3.3 mg/kg bw) was determined and includes a safety factor of 100 to allow for extrapolation from the LOEL to a NOEL. In one study, designed to explore anti-proliferative and secretory endpoints in the endometrium, women were treated with 300 or 600 mg/day of fine particle progesterone for two weeks following a thirty day pretreatment with oestrogen. The group treated with the 300 mg dose showed incomplete conversion of the uterus to full secretory activity whilst the group receiving the 600 mg dose did. In an additional studies using 200 or 300 mg oral doses of progesterone for one or five years, there was no evidence of endometrial hyperplasia or carcinoma. In addition, it was stated that a single oral dose of 200 mg fine-particle progesterone produced concentrations of progesterone in blood similar to those found during the luteal phase of the ovulatory cycle. While these data indicate that the daily exposure from consuming hormonetreated beef is well below the ADI, there is some concern regarding determination of the ADI. First, neither the actual data nor reference to a peer-reviewed publication was provided. Second, the dose-response was limited to two doses and the ADI was estimated from just a single dose rather than a curve derived from all the data available. The tolerance levels for progesterone levels in uncooked tissues of steers and calves established by the FDA (Ref.: *Code of Federal Regulations (CFR) 21, Part 556, Tolerances for residues of new animals drugs in food*) are:

Tissue	Progesterone (μg/kg)
Muscle	3
Liver	6
Kidney	9
Fat	12

Based on these levels, consumption of 500 g/day of beef (300g muscle, 100g liver, 50g each of kidney and fat) would result in exposure to approximately

2.6 μg/person/day. This amount represents approximately 1-2% of the daily production rate for progesterone of 150 μg/day estimated for prepubertal boys, and approximately 0.3% of the maximum excess exposure to progesterone estimated to occur upon consumption of meat from hormonetreated cattle (Table A3, Annex). However, there is considerable uncertainty associated with the validity of the daily production rate data. It is possible that this value has been over estimated by one to two orders of magnitude, in which case excess progesterone intake from hormone-treated beef could at best exceed the 1% FDA safety margin and at worst be greater than that naturally present.

- **1999 SCVPH opinion.** *Progesterone Levels in Human Blood:* The data show that premenopausal women have the highest levels of endogenous progesterone (Table 1, section 3.1). Progesterone production rates in premenopausal women during the follicular phase have been determined to be approximately 418 μg/day (JECFA, 1987 monograph). During pregnancy, progesterone production rates during late pregnancy have been determined to be approximately 94,000 ug/day (JECFA, 1987 monograph). In men, the daily production rate for progesterone is approximately 416 μg/day, respectively (JECFA, 1987). In prepubertal boys, the progesterone production rate has been reported to be 150 μg/day (JECFA, 1987). Thus, prepubertal and postmenopausal females and prepubertal and adult males have the lowest levels of endogenous progesterone and thus would represent the individuals most likely to be at increased risk for adverse health effects that might be associated with exposure to exogenous sources of oestrogens.

- **1999 SCVPH opinion (page 55-56).** 4.4. Trenbolone. Trenbolone acetate (TBA), 17β-hydroxyestra-4,9,11-triene-3-one, is a synthetic steroid with anabolic properties. It is 8 to 10 times as potent as testosterone (Bouffault and Willemart, 1983). In animals, TBA, alone or in combination with 17ß-ooestradiol, is used to improbe weight gain and feed efficiency. This effect is most likely a consequence of the anabolic acion of this androgen. The various TBA-containing implants, their composition, and target animal are shown in Tables A1 and A2.

  4.4.1. Pharmacokinetics and biotransformation of trenbolone in animals. TBA is administered by subcutaneous implantation in the ear. The ear, along with any residual drug, is discarded after slaughter. The dosage of TBA varies with manufacturer of the implant, ranging between 40 and 300 mg per animal (JECFA, 1988). TBA upon entering the circulatory system is rapidly hydrolyzed to its active free form, 17β-trenbolone (TBOH). In the bovine species, the 17α-epimer is the major metabolite occurring in the excreta, bile and liver; the 17β-epimer is the major metabolite occurring in muscle (Jouquey et al., 1983). Elimination in the bile and urine occurs following conjugation, predominately to glucuronic acid (Pottier et al., 1979; Pottier et al., 1981). Also in blood plasma, conjugated TBOH has been determined; 56 concentrations were 13% of those of free TBOH. In addition a number of other metabolites have been identified in bile. However, only trendion seems to occur in some qualitative amounts. In 1978, Ryan and Hoffman (Ryan and Hoffman, 1978) reported remarkable discrepancies in residue concentrations as determined by radiotracer studies and RIA; they concluded that the much lower values obtained by RIA were due to the formation of covalently bound nonextractable residues. This observation was further substantiated (Evrard and Maghuin-Rogister, 1988), and in vitro studies (43) have demonstrated the involvement of hepatic cytochromes P450 in the formation of these type of residues. The metabolism of TBA appears complex and species dependent. Further investigations of both the metabolic

fate and the chemical nature of the covalently bound residues is warranted (Metzler, 1999).

- **1999 SCVPH opinion.** *4.4.2. Trenbolone disposition in the target animal.* TBA is rapidly metabolised to its free active form, alpha and beta TBOH. In cattle, the β-epimer is the major metabolites in muscle. The concentrations of α- and β-TBOH, free and conjugated have been measured in muscle, liver, kidney and fat of treated cattle at various times after implantation. Table 8 shows the residue values for these tissues at the time after implantation where the highest level of ß-TBOH was detected in muscle. (*Table 8: Residue Levels (ng/kg) of α- and β-TBOH (free + conjugated) in tissues of treated cattle *30 days post implant; + free + conjugate; Data from JECFA, 1987).*

- **1999 SCVPH opinion.** *4.4.3. Pharmacokinetics and biotransformation of trenbolone in humans* The metabolism of trenbolone in humans has not been extensively studied. In one study, Spranger and Metzler (Spranger and Metzler, 1991) examined the disposition of 17-β-trenbolone in a single human subject administered 0.04 mg/kg body weight. Urine was collected in fractions for 72 hours after ingestion. The fraction of the first 3-h urine contained the highest concentration of radioactivity and was used for the analysis of metabolites. Of the urinary material, 54 % was present as glucuronides, which contained mostly 17α-trenbolone, 17β-trenbolone and trendione. At least five other polar metabolites, presumably hydroxylated products, were detected in smaller amounts. A total of 54% of the administered radioactivity was found in the urine after 26 hours, and 63% after 72 hours (Spranger and Metzler, 57 1991). Further analyses of the formation of polar metabolites of trenbolone is essential to the assessment of the risk of repeated dietary exposure of humans to this compound.

- **1999 SCVPH opinion.** *4.4.4. Assessment of exposure to trenbolone from consumption of hormone-treated beef.* Since TBA does not occur naturally, by definition endogenous levels in humans should be zero. Thus, any residues detected in the meat of treated cattle represent excess exposure to individuals consuming the meat. The ADI for trenbolone acetate recommended by the JECFA(1987) for humans was 0-0.1 µg/kg body weight based on a non-hormonal effect level of 2 µg TBA/kg in a study in pigs. In 1988 the Expert Committee on Food Additives (JECFA), using this same non-effect level established a temporary ADI of 0.01 µg TBA/kg body weight (0.7 µg/70 kg person), and recommended a temporary Acceptable Residue Level of 1.4 µg/kg bovine meat for β-TBOH on the basis of consumption of 500 g meat by a 70 kg person. The FDA (*CFR 21, Part 556, Tolerances for residues of new animals drugs in food*) has set tolerance limits for TBA levels in uncooked tissues of cattle.

Tissue	TBA (µg/kg)
Muscle	50
Liver	100
Kidney	150
Fat	200

Based on these levels, consumption of 500g of meat/person/day (comprised of 300g muscle, 100g liver, 50g kidney and 50g fat) the acceptable daily consumption of TBA could reach 43 µg/person/day, an amount considerably greater than recommended by the JECFA. This value greatly exceeds the recommended ADI. The toxicological

issues of concern include endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects. Specific hazardous effects are detailed below.

- **1999 SCVPH opinion.** *4.4.5. Mutagenicity and genotoxicity* 17β-Trenbolone (β-TBOH) is a synthetic androgen. 17α-trenbolone (α-TBOH) is a metabolite formed in cattle. Both, the parent compound and its metabolite (α-TBOH), have been extensively tested for their mutagenic/genotoxic potential. The results are summarized as follows (table 9).

- **1999 SCVPH opinion. (***Table 9: Mutagenicity testing of trenbolone and its metabolite)*. Both 17α- and 17β- TBOH gave the same results. As the 17α-metabolite is more weakly androgenic, it might be concluded that the genotoxic effects of TBOH are not related to their hormonal activity. The ability of 17β-TBOH to transform Syrian hamster embryo cells has to be noted (Lasne, et al., 1990), although another laboratory found negative results at all concentrations tested (Tsutsui, et al., 1995).

- **1999 SCVPH opinion.** *4.4.6. DNA adducts and DNA damage.* Covalent binding of [3H]17β-TBOH to DNA was observed after incubation with rat liver postmitochondrial supernatant *in vitro* and in rats *in vivo* after oral or i.p. administration (Lutz et al., 1988). Binding of TBOH to rat liver DNA was also observed by Barraud et al. (1984) and Petit et al. (1989). Formation of DNA adducts is also observed in rat hepatocytes cultured with 30 μM β-TBOH (Metzler, 1999).

- **1999 SCVPH opinion.** *4.4.7. Carcinogenicity.* Feeding of high doses of Trenbolone acetate (TBA) to mice induced a significant amount of liver hyperplasia and tumors; in rats a slight increase in islet-cell tumors of the pancreas was observed (WHO Technical Report No. 696, 1983). A 2-year carcinogenesis bioassay in male and female rats and mice did not provide definitive results on the carcinogenicity of β-TBOH (mentioned in Schiffman et al., 1988). In humans, no data are currently available to assess the carcinogenicity of trenbolone. In conclusion, in consideration of the lack of in vitro short-term assays on mutagenicity and genotoxicity of other TBOH metabolites other than α-TBOH, and in consideration of the equivocal results of cell transformation assays and the in vivo studies, the available information is insufficient to complete a quantitative risk assessment. It has also to be noted that a considerable fraction of TBOH residues seems to be covalently bound to tissues.

- **1999 SCVPH opinion.** *4.4.8. Effect of trenbolone on growth and reproduction.* Deleterious effects of trenbolone acetate exposure were reported in the reproduction of both male and female mammals of various species (JECFA, 1988). In the adult male, trenbolone acetate administered by ingestion, injections or implants induces a decrease in testis, seminal vesicle and prostate weights and alterations in spermatogenesis. In the adult female, such treatments induce virilization and alteration or suppression of ovarian cycles. In a study involving women volunteers given i.m. doses of 10 mg trenbolone acetate every-other-day during 14 days, disturbances of the menstruation cycle have been reported. Some data in rodents indicate that administration of trenbolone acetate during the intrauterine or/and perinatal period alters the reproductive function in adults. In a multi-generation study, it has been shown that trenbolone acetate, administered to female rats at dietary concentrations of 3 and 18 ppm between 2 weeks before mating and 3 weeks after birth of youngs exerts effects on reproductive performance which are more marked in F2 pups than in F1 pups of a comparable age. Indeed, female F1 pups from F1-treated

parents show signs of virilization, a delay in the mean vaginal opening and the presence of occlusive strands in the vagina or incomplete vaginal opening. Male pups show a delay in the occurrence of testicular descent and a decrease in weights of seminal vesicles, prostate, testes and epididymis. In addition in F2 from both sexes, the adrenal weight is also decreased (JECFA, 1988). These data do not allow a realistic assessment of a dose response relationship.

- **1999 SCVPH opinion.** *4.4.9. Effects of trenbolone on the immune system.* Investigations on the effects of trenbolone on the immune system are very limited. A slight, but non statistically significant, immuno depression was seen in male calves given SC implants of trenbolone acetate (140 mg). A statistically significant change was observed when a combination of trenbolone acetate and oestradiol (20 mg) was used. No such change was seen with oestradiol alone. In female calves no such effects were observed (Gropp et al., 1975). In conclusion, this information is insufficient to assess the possible impacts of low levels of trenbolone in meat and meat products on consumers.

- **1999 SCVPH opinion.** 4.5. Zeranol. Zeranol (α-zearalanol) is an oestrogenic derivative of the mycooestrogen zearalenone. This oestrogen depresses the endogenous gonadotropins, luteinizing hormone and follicle stimulating hormone. Zeranol binds to the oestrogen receptor in swine, rats and chickens with a binding affinity similar to that of DES, which is much greater than that of oestradiol (Fitzpatrick, et al., 1989). In rat liver, zeranol was shown to bind to the oestrogen receptor and to DNA in a manner similar to that of oestradiol (Mastri, et al., 1986). Dietary administration of castrate female Rhesus monkeys for two consecutive days provided a no-effect level of 1 mg/kg/day (Fuller, et al., 1982). The zeranol-containing implants and target animals are summarised in Table A2 of the Annex.

- **1999 SCVPH opinion.** *4.5.1. Pharmacokinetics and biotransformation of zeranol in animals.* The half-life of zeranol plus its metabolites in the blood was 26 h in New Zealand rabbits and 18 h in Rhesus monkeys (Migdalof, et al., 1983). Glucuronide and sulfate conjugates were found in the urine. Both zearalenone and taleranol (isomeric β-zearalanol) have been found as metabolites of zeranol in cattle (Sharp and Dyer, 1972; Duchatel and Maghuin-Rogister, 1985; Jansen, et al., 1986; Kim, et al., 1986). When zeranol was metabolized by uninduced or Arochlor-induced rat liver microsomes, five new metabolites, tentatively identified as monohydroxylated derivatives, and small amounts of taleranol and zearalenone were observed (Metzler, 1999). Three of the five monohydroxylated derivatives of zeranol were also observed with bovine liver microsomes.

- **1999 SCVPH opinion.** *4.5.2. Zeranol disposition in the target animal.* In a study of cattle implanted in the ear with 30 mg of tritium-labeled zeranol, the tissue residues peaked at 5-15 days and then slowly decreased (Tarr, et al., 1984). At 65 days, approximately 60% of the initial dose remained at the implant site. The maximum residue level occurred in the liver and never exceeded 10 μg/kg, whereas the residue level in muscle did not exceed 0.13 μg/kg. In cows implanted with Ralgro (36 mg) and slaughtered 70 days later, the average values of zeranol determined by a radioimmunoassay were 0.127 μg/kg in muscle, 0.184 μg/kg in fat, 0.299 μg/kg in liver and 0.157 μg/kg in kidney (Dixon and Mallinson, 1986). In steers implanted with Ralgro (36 mg) and slaughtered 70 days later, the levels of zeranol in liver, kidney, muscle and fat were 0.200, 0.126, 0.725 and 0.073 μg/kg (Dixon, et al., 1986).

- **1999 SCVPH opinion (page 60).** Male pups show a delay in the occurrence of testicular descent and a decrease in weights of seminal vesicles, prostate, testes and epididymis. In addition in F2 from both sexes, the adrenal weight is also decreased (JECFA, 1988). These data do not allow a realistic assessment of a dose response relationship.

- **1999 SCVPH opinion.** The convention used by JECFA as the basis for determination of daily consumption of hormones is based on eating 500 g of meat per day (300g muscle, 100g liver, 50g kidney and 50 g fat). Based on this and the acceptable oestradiol levels in beef shown in Table 3, total daily consumption of currently acceptable levels of oestradiol would be 102 ng. This value represents approximately 1-2% of the currently used calculated daily production rates for oestradiol in prepubescent children. As mentioned previously in the *Exposure Considerations Section*, the daily production rate for oestradiol was estimated to be 6 μg/day oestradiol in boys. These daily production rate (PR) values are determined by the formula: PR (μg/day) = plasma concentration (μg/ml) x metabolic clearance rate (MCR, ml/day). However, there are two potential problems with these values. First, as mentioned previously (*Exposure Considerations Section)*, determination of plasma concentrations of oestradiol is subject to considerable variability, relative insensitivity given its low levels in children, and interference. A new, highly specific, more sensitive assay for oestradiol indicated that blood oestradiol levels in girls may be as much a 13 fold less and in boys 100 fold less than previous determinations using RIAs indicate. Second, it does not appear that MCRs have ever been determined directly in children. Rather, it appears as if MCR values from adult women were used in the calculations of the PRs for children (Andersson and Skakkebaek, 1999). This approach may or may not be valid given the known differences in levels of SHBG (higher in children, which would reduce clearance), and likely differences in uptake and metabolism, etc. Given these issues, it is possible that the safety margin for oestradiol exposure used by the FDA may be in error and that acceptable levels of hormone residues in beef could be much lower. (Similar concerns apply to progesterone and testosterone). The median level of excess exposure to oestradiol from consuming meat from hormone-treated cattle is 6.8 ng/person/day (calculated from Table A3, Annex, range 1 to 84 ng/person/day). For comparative purposes, assuming 100% absorption and a whole blood volume of 78ml/kg body weight, for a 40 kg child, based on the median value for excess oestrogen exposure, the blood concentration calculates to be 2.2 pg/ml (1 to 26 pg/ml). If the blood oestrogen levels are 100 fold lower than previously determined and the MCR too high by a factor of 10, the oestradiol daily production rate could be as low as 6 ng, and 1% of this would be 60pg. Thus, the FDAs acceptable daily intake (102 ng/person/day, see above) could exceed the daily production rate of oestradiol by 1,700 fold. While there is some experimental evidence in support of the currently used blood levels of oestradiol being 100 fold too high (Klein et al., 1994), the other assumptions used in coming to this conclusion may be too conservative. Thus, if absorption is reduced to 10% and the MCR for children is only 1/2 that of adults, the FDA acceptable daily intake could still be 85 fold too high. Given all of the uncertainties in these estimates, it appears that the data are insufficient to form the basis of a sound risk assessment. Clearly, this is an important area for additional research.

- The question is whether the risk assessments of the five hormones by JECFA in 1987/1989 and of MGA by the US and Canadian authorities were based on evidence focusing specifically on the lack of carcinogenic, genotoxic, or endocrine effects of

> the residues of these hormones in bovine meat and meat products? The risk assessment by JECFA in 1987/1989 was based on hormonal effects only and no excess exposure was envisaged, the genotoxic and carcinogenic potential of residues in meat and meat products was not considered. More recent work on biotransformation mediated genotoxicity (cited also in the JECFA 199 report) shows that no threshold can be defined either for the endocrine, developmental, immunological and neurobiological effects or for their potential immunotoxicity and carcinogenicity. This statement is also made in the light of the emerging concerns of the effects of hormones at different stages of life and the accumulating epidemiological findings on tumor incidence as summarized by IARC. The SC also acknowledged that recent findings on the metabolism based genotoxicity of 17-ß oestradiol (see chapter 2.5 of the 1999 report) it has to be stated that the assumption that the carcinogenic potential is exclusively related to the hormonal activity is no longer valid. In addition it is worthwhile mentioning recent improvements in analytical techniques applied in the measurement of physiological hormone levels. The introduction of more sensitive and specific bioassays/oestrogen receptor assays (as outlined in detail in the text of the report) indicated that a critical reappraisal of the endogenous hormone levels in certain segments of the human population, such as prepubertal boys and girls is required.

127. The 2002 opinion of the SCVPH moreover considered the report on melengestrol acetate prepared by the 54th meeting of JECFA.

128. In summary, the European Communities considers that the assessments of JECFA mentioned above have suggested that it is unnecessary to set maximum residue limits (MRLs) for oestradiol 17ß, testosterone and progesterone because they considered that residues resulting from the use of these substances as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health. But for zeranol and trenbolone acetate MRLs have been proposed by JECFA.

129. However, as already explained the above-mentioned JECFA reports found that oestradiol 17ß "*has genotoxic potential*" and that the evidence for progesterone was interpreted "*on balance*" as not having genotoxic potential. On the basis of these findings, JECFA did consider for the first time that ADIs were necessary to be fixed but not MRLs, because of the endogenous production of these natural hormones and the difficulties in applying the available detection methods in order to determine the origin of any residues in meat. But the European Communities could not adopt the risk management options proposed by JECFA, because the scientific risk assessment of the SCVPH did not come to the same conclusions as those of JECFA (see the passages from the SCVPH opinion listed above). One of the difficulties of the JECFA reports, for instance, is that JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not. Therefore, after the examination of the full range of risk management options and taking into account the potential advantages and disadvantages as well as consequences and feasibility of risk management options (in particular that of control), the European Communities regulatory authorities concluded that the prohibition of the use of hormones for growth promotion within the European Communities and the exclusion of import of meat derived from animals treated with hormonal growth promoters was the most appropriate measure in order to protect its consumers from the risks identified from excess intake of hormone residues and their metabolites and the potential for abuse, *inter alia*, through non-observance of good husbandry practices. In other words, the European Communities came to the conclusion that the JECFA's recommendations could not achieve the level of health protection considered appropriate by the European Communities in its territory from residues of these hormones under realistic conditions of use for animal growth promotion.

Q23. Does the European Communities agree that the re-evaluation of the risks of progesterone by the Committee for Veterinary Medical Products in 1999 concluded that this hormone is safe when used according to good veterinary practice? If so, has the European Communities taken this conclusion into account in its overall risk assessment process? If not, why has this conclusion not been considered? What are the arguments that have precluded this conclusion from being used as the basis of the EC's measure for progesterone (US first written submission, para. 128)?

130. The European Communities would like to recall that the Appellate Body has reversed the panel's findings on the issue concerning the occasional use of the naturally occurring hormones for therapeutic or zootechnical purposes.[39] Therefore, arguments of this kind by the defending parties in the context of these proceedings attempt to reintroduce a debate that they have lost at the Appellate Body level. A short reply to this question, therefore, is that this issue is now irrelevant.

131. However, the European Communities will provide some information on this question. Indeed, the SCVPH opinions, and in particular the opinion of April 2002, have indeed taken the CVMP's 1999 assessment on progesterone into account, notably in the light of the new scientific studies available by 2002. Hence, the European Communities' overall risk assessment of progesterone use as growth promoter in cattle has duly taken this opinion into account, as evidenced in recital 7 of the new regulation on progesterone (Commission Regulation (EC) no 1873/2003/EC mentioned above),[40] which explicitly cites the CVMP conclusions and explains how they are taken into account, as a basis for the new provisional ban on progesterone.

132. The arguments that have precluded the conclusion of the CVMP's from being used as the only basis of the EC's measure for progesterone as a growth promoter are the following : First, new scientific evidence had appeared since, and the SCVPH opinions, within their own assessment for its use as a growth promoter, had identified risks, which were incompatible with the level of health protection which the European Communities applies to these hormones when intended to be used for animal growth promotion purposes.

133. Secondly, it would be more correct to states that the "qualifier" of the CVMP conclusion would rather be when progesterone is used in veterinary *medicinal* products authorised in accordance with the relevant Community legislation, which would exclude "over the counter" products freely available to a layman, outside any veterinary control. In reality, the CVMP risk assessment on the possible need to establish MRLs for progesterone was evaluated only for therapeutic or zootechnical purposes and *not* for animal growth promotion purposes, as the defending parties wrongly argue. The assessments of the risks from the CVMP and from the SCVPH were, therefore, for different purposes and it is not possible to extrapolate the conclusion of one Committee made for one specific use, as explained above.

Q24. Does the European Communities agree with the United States that a risk assessment includes four steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization? What is the EC's response to the US argument that the EC failed to proceed from identifying hazards to characterizing hazards and to assessing the exposure in order to demonstrate a specific risk to consumers (first US written submission, para. 42)?

[39] *See* Appellate Body Report, *EC – Hormones*, at paras. 221-225.

[40] Commission Regulation (EC) No 1873/2003 of 24 October 2003 amending Annex II to Council Regulation (EEC) No 2377/90 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

134. The European Communities does not agree with the United States unfounded claim that the EC would not have followed internationally recognized standards of risk assessment (in the narrow or strict sense mentioned in the Codex Alimentarius Commission principles on risk analysis, as explained with the reply to Question No 16 above), and find this kind of criticism unfounded and irrelevant.

135. First, it has to be clarified that, as defined by the Codex Alimentarius Commission, risk assessment is normally considered to be only the first component of a three part process, known as risk analysis. It is the scientific process which is intended to provide the competent regulatory authority with the information required to allow it to decide on the measures necessary to reduce the risk from a particular hazard to a level that is considered acceptable in its territory and under the conditions prevailing therein.

136. The United States and Canada make little or no reference to risk management, which is the second component and an integral part of the internationally agreed process of risk analysis, which has to be completed *after* the completion of the four steps of risk assessment.

137. This second part of risk management is the process "of weighing policy alternatives in the light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures". And as the Appellate Body indicated in its report, in agreeing with the European Communities, setting the level of health protection is the autonomous right of the authority responsible for risk management.

138. For instance, as regards the use of these hormones for animal growth promotion in the circumstances prevailing in the European Communities, its authorities have determined at the risk management stage of the risk analysis, on the basis of the scientific risk assessments that the SCVPH had performed on its behalf, that the addition to the food chain, whether of naturally occurring or synthetic hormones, is an avoidable risk, which needs to be prevented in order to meet the chosen level of health protection.

139. But to come back to the scientific assessment of the risks itself, as the first component of risk analysis, it is performed in the European Communities by advisory bodies composed of independent experts, such as the SCVPH, as it is laid down in the relevant legislation that is generally applicable. The United States cites four general steps which are identified internationally (albeit not always with the name cited by the United States), as being relevant for the risk assessment (at the first stage in risk analysis), but not the risk analysis itself.

140. The European Communities of course follows these four components or steps, as does all advisory bodies performing internationally recognised assessments of risks.[41] It has to be noted, however, that which ever approach is followed, they are all based on a deterministic approach to risk characterisation (the level of exposure amounts proportionally to the level of risk for a given hazard), have serious limitations in non-linear situations, such as in the current case regarding these hormones. Here, the risks are embedded in changes in exposure to biologically active molecules which may, within minute differences in their bioavailability, have dramatic effects, such as turning on or off complete developmental programs of the human genome, or inducing pathological conditions. This is a classical non linear situation, which is poorly addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission.

[41] For instance, another internationally recognised approach for risk assessment is made of three steps: hazard characterisation (in fact the severity of each identified hazard), probability of occurrence, and the risk being then conceptually characterised as the product of the hazard (danger) by its probability of occurrence.

141. The United States also fails to identify that, for instance, the recommendation to perform an exposure assessment is to be formalised to an actual identification of exposure, only when such exposure assessments can be made because the data are available, which, in this case, as largely demonstrated by the opinions of the SCVPH and the available scientific evidence, is often not the case in the current state of available pertinent information.

142. The USA criticism is also irrelevant in the present context, where the risk assessment at the basis of the new Directive precisely follows these four steps, enabling it to identify different levels of risks presented by different uses, and the new Directive then adapts the management of these risks accordingly, which incidentally is not the case in the defending members.

143. In addition to the above rather general considerations, in order to confirm that the European Communities has addressed in its risk assessment the four steps mentioned by the United States, it would suffice to draw the attention of the Panel to the table of contents (Index) of the SCVPH 1999 opinion, which is reproduced below and identifies all these steps, one after the other for all the six hormones, each of which then being explored in detail and in substance in the body of the SCVPH report: the title for each entry speaks for itself.

144. Indeed, the whole of section 2 identifies and characterizes more than twelve serious hazards due to these hormones, and section 3 addresses thoroughly exposure assessment, as indicated explicitly in its title. Section 4 then addresses individually each of the six hormones, and goes into the characterisation of each risk, with the relevant exposure assessment for each of the hazard previously identified and characterised and which is relevant for that hormone. Section 5 summarizes the overall risk characterization of the opinion.

Q25. Could the European Communities explain the hazard characterization in terms of the Opinions. Is dose-response assessment a necessary approach of hazard characterization in the EC's view? Or, is there an alternative approach which replaces the dose-response assessment? What have the Opinions done in this respect?

145. Hazard characterisation, as the words denote, is the step whereby a generally identified hazard (death, spontaneous abortion, carcinoma, breast cancer, autoimmune disease, developmental pathology of reproductive organs, DNA adduct formation, etc.) may be characterised in connection with the uses of the six hormones.

146. The short answer to the second part of the question is that a dose-response assessment is a recommended approach to characterise specific hazards **when one can do it**, but is by no means a compulsory nor a necessary approach. In fact, the Appellate Body has clearly judged that a risk assessment can be either qualitative or quantitative and has rejected the contention that a minimum magnitude of risk was necessary (at para 186 of the Appellate Body report).

147. But in any case, as regards the six hormones in question, the scientific opinions of the SCVPH have made a hazard characterisation for each of these hormones, as it can easily be verified by reading its 1999 opinion. In particular, it has identified a number of hazards and has characterised for the bioactive molecules at stake in these hormones that the hazards, such as for example genotoxic effects, may manifest themselves with very long time lapses between dose exposure and response, and it may often not be possible to measure properly the relevant dose-response impacts of the hormone or hormone residues. The 1999 SCVPH states, *inter alia*, on this issue:

> "The potential adverse effects on human health from residues in bovine meat and meat products include endocrine, developmental and neurobiological, immunological as well as carcinogenic, genotoxic and immunotoxicological effects as described in the report and addressed in the executive summary. These effects can be attributed to

> either the parent compound or the metabolites. Residue analysis has focussed in the past on the quantification of the amounts of residues of the parent compounds and those metabolites exerting hormonal activity. Recent data indicate that other metabolites occur additionally which have genotoxic activity. For example, 17-ß oestradiol can be metabolized to 2-OH, 4-OH and 16α-OH oestrogens. Particular the 2-OH, and 4-OH oestrogens have been found to be directly or indirectly genotoxic. This implies that 17-ß oestradiol may act as tumor initiator as well as tumor promoter. These findings are in agreement with epidemiological data and resulted in the classification of 17-ß oestradiol as human carcinogen (Group 1 according to the IARC classification). This implies that any excess exposure towards 17-ß oestradiol and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the population which have been identified as particularly sensitive such as prepubertal children. It should be noted that for these genotoxic metabolites in bovine tissues, no threshold level can be established. In addition, no threshold level can be established for any of the hormonally active compounds and metabolites which might exert endocrinal, developmental and neurobiological, immunological or immunotoxicological effects.
>
> With the exception of 17-ß oestradiol, the currently available information for testosterone, progesterone and the synthetic hormones zeranol, trenbolone and particularly MGA has been considered inadequate to complete an assessment.
>
> This conclusion is based upon:
>
> – incomplete data on the biotranformation pathways of these compounds and the possible biological activity of the metabolites formed in bovine tissues as, for example, testosterone might be aromatized to oestradiol.
>
> – lack of data on the potential genotoxicity of these metabolites in consideration of the current state of the art for genotoxicity testing as indicated in the answer to question 2 (a).
>
> – insufficient data on immunological and immunotoxical effects.
>
> Based on experimental and epidemiological data, testosterone and progesterone have been classified by IARC as Group 2 substances - probable/possible carcinogens in humans. No epidemiological data are available for zeranol, trenbolone and MGA (melengesterol acetate) although residues of hormonally active compounds in (poultry) meat have been shown to exert an oestrogenic response in prepubertal children in certain countries.
>
> Thus, no final conclusions can be drawn with respect to the safety of at least five out of the six substances under consideration, until the above described issues have been clarified. For oestradiol genotoxicity has already been demonstrated explicitly."

148. Moreover, it has done this hazard characterisation as regards also the particularly vulnerable segments of the population that may be exposed to these identified hazards, that is prepubertal children. The 1999 SCVPH states, inter alia, on this issue:

> "In acknowledging the recent findings on the metabolism based genotoxicity of 17-ß oestradiol (see chapter 2.5 of the report) it has to be stated that the assumption that the carcinogenic potential is exclusively related to the hormonal activity is no longer

valid. In addition it is worthwhile mentioning recent improvements in analytical techniques applied in the measurement of physiological hormone levels. The introduction of more sensitive and specific bioassays/oestrogen receptor assays (as outlined in detail in the text of the report) indicated that a critical reappraisal of the endogenous hormone levels in certain segments of the human population, such as prepubertal boys and girls is required."

Q26. Is "exposure assessment" a necessary element of the risk assessment? Please explain the EC exposure assessment in terms of the Opinions? Has the European Communities conducted an analysis comparing the actual residues of the hormones in meat from cattle not treated with growth-promoting hormones with those in meat from cattle treated with hormones according to good veterinary practice? What is the health risk to humans associated with the pathway of oestradiol 17 β used in animals for therapeutic and zootechnical purpose?

149. The last part of the question on therapeutic and zootechnical purposes, apart from being legally irrelevant in view of the Appellate Body findings mentioned above, has been largely addressed in the replies to the previous questions, in particular question 20, and will not be addressed here anymore.

150. This being said, in the case of the six hormones, the European Communities has performed exposure assessments systematically when it was able to do so, as detailed in the three SCVPH opinions.

151. As regards the question whether the European Communities has performed an "analysis of comparing the actual residues of the hormones in meat from cattle not treated with growth-promoting hormones with those in meat from cattle treated with hormones according to good GVP", the European Communities has already explained with its reply to Question 17 above, that it considered in its assessment the potential risks resulting from the actual residues from non-treated as well as treated animals for growth promotion, and came to the conclusion that under realistic conditions of use such residues from treated animals for growth promotion do pose a higher risk and could not achieve the level of protection it has considered appropriate in its territory. As discussed before, for the purposes of exposure assessment from the residues of these hormones, it is not so much necessary to compare (if it were only possible!) the two situations and then try to quantify how much one is more risky than the other and to what measurable level the risk is likely to occur, but rather to assess a situation of additive risks arising from the cumulative exposures of human to multiple hazards, in addition to the endogenous production of some of these hormones by the animals and the human beings. For those reasons, the European Communities has determined, at the risk management stage of the risk analysis, on the basis of the scientific risk assessment that the SCVPH had performed on its behalf, that the addition to the food chain of any level of residues from the exogenous administration of these hormones to animals for animal growth promotion purposes is an avoidable risk, which needs to be prevented in order to meet its chosen level of protection.

152. Furthermore, one would also like to know what exactly the defending members have done in this respect, since the risk assessments they claim to have performed are very old by today's standards (dating from the 70's in most cases). Have the United States and Canada, or any other WTO member, actually done this kind of exposure assessment, when they decided to authorise these hormones for animal growth promotion purposes? Could they communicate the results of their assessment on this specific point to the Panel and other parties to this dispute?

153. Finally, it should again be clarified that whereas the original Panel concluded that "potential" means "probable", the Appellate Body concluded (at para. 184) that the use of this term gave cause for concern, noting that this introduces a quantitative dimension to the notion of risk, also noting that

the ordinary use of "potential" relates more to the word "possible". Otherwise, it argued, there would be an implied need for a quantitative assessment of risk. The Appellate Body clearly judged that a risk assessment can be either qualitative or quantitative. Thus, the panel implication in the hormones case that there must be a minimum magnitude of risk was rejected by the AB (at para. 186). The submissions from US and CAN in the context of the present dispute, however, seek again to impose the need for a quantitative assessment and a minimum level of risk. This has failed once and should fail again. The US and CAN submissions misrepresent certain other elements of a risk assessment. For example, the US 1st written submission (at para. 143) equates hazard characterisation with dose response. Although the Codex Alimentarius recommendations on risk analysis urge that a dose response assessment should be carried out where possible, this is not the central issue in hazard characterisation. According to Codex Alimentarius, the central element is "---a qualitative or quantitative description of the severity and duration of adverse effects ---". The EU has demonstrated the potential adverse effect, but has been unable to quantify it in a precise manner. No one, on the other hand, can doubt the severity of a carcinogenic effect, both pathologically and psychologically. It is quite clear that the potential effect of a carcinogenic substance is substantially greater than, for example, the effects of most microbiological agents. It is clear that this risk can be avoided or at least not added to the burden resulting from the naturally-occurring hormones and residues from other sources. There is no good reason to deny the consumer in the European Communities this higher level of protection.

Q27. Could the European Communities provide the Panel with the relevant data and analysis leading to the conclusion that "misplaced implants and repeated implanting seem to occur frequently, represent a considerable risk that highly contaminated meat could enter the food chain" in the SCVPH's 2002 review Opinions (US first written submission, para. 145)?

154. There was indeed a specific study taken into account in the SCVPH 2002 opinion that has addressed this issue. The European Communities provided it to the Panel with the exhibits attached with its reply to question no 16 (as Exhibit EC-6 (US) and Exhibit – EC 4 (CAN)). It is the study concerning the application of anabolic agents to food producing animals - health risks through disregard of requirements of good veterinary practice. This multifaceted study has given rise to a number of scientific publication in peer reviewed journals. They are the following:

(1) "Detection of melengestrol acetate residues in plasma and edible tissues of heifers", The Veterinary Quarterly 21: 154-158, 1999.

(2) "Detection of anabolic residues in misplaced implantation sites in cattle", Journal of AOAC International 83(4); 809-819, 2000.

(3) "Suppression of androstenone in entire male pigs by anabolic preparations", Livestock Production Science- 69: 139-144, 2001.

(4) "A sensitive enzyme immunoassay (EIA) for the determination of Melengestrol acetate (MGA) in adipose and muscle tissues", Food Additives and Contaminants 18(4):285-291, 2001.

(5) "Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and to the bovine progestin receptor", APMIS 108: 838-846, 2000.

(6) "Dose-dependent effects of melengestrol acetate (MGA) on plasma levels of estradiol, progesterone and luteinizing hormone in cycling heifers and influences on oestrogen residues in edible tissues", APMIS 108: 847-854, 2000.

(7) "Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: Effect of the implant preparations Finaplix-H®, Ralgro®, Synovex-H® and Synovex Plus®", APMIS 109: 53-65, 2001.

(8) "Tissue-specific expression pattern of estrogen receptors (ER): Quantification of ER_ and ER_ mRNA with real-time RT-PCR", APMIS 109: 345-355, 2001.

Q28. Has the European Communities considered the general low bioavailability of the six hormones at issue in its risk assessment? What is the EC's response to the US argument that JEFCA's risk assessment has indicated that oestradiol is generally inactive when given orally to humans (5% bioavailability)? In what way does this factor of low bioavailability affect the exposure assessment? Could the European Communities point out its analysis concerning the occurrence of health risk to consumers via the specific pathways at issue?

155. Yes, the general bioavailability of the six hormones at issue was considered in the risk assessment of the European Communities. The 1999 opinion of the SCVPH explains for each of the six hormones the evidence relating to their bioavailability. For instance, as regards oestradiol, the 1999 opinion states (on page 36) that:

> "4.1.4. Pharmacokinetics and biotransformation of 17β-oestradiol in humans.
>
> The oxidative metabolism of endogenous oestrogens is known to occur at several positions including carbons C-1, C-2, C-4, C-6, C-7, C-11, C-14, C- 15, C-16, and C-18. The major oestrogens detected in serum and urine are the 2-hydroxylated metabolites. The liver is the primary site of oestrogen metabolism, where rates of 2- and 16α-hydroxylation, catalysed by P4501A2, P4503A3 and P4503A4, greatly exceed that of 4-hydroxylation. Because 4- hydroxylated metabolites represent only a small percentage of the total amount of oestrogens detected in the urine, 4-hydroxylation has been considered a minor metabolic route of metabolism. However, it is now understood that extrahepatic tissue 4-hydroxylation of E2 may play a significant role in oestrogen homeostasis. In several organs which are sites of oestrogen-induced tumours, the rate of E2 4-hydroxylation equals or exceed the rate of 2-hydroxylation, and in comparison to normal tissue, elevated E2 4-hydroxylase activity has been observed in samples prepared from breast and uterine tumours. In humans, cytochrome P4501B1 has been identified as the most significant E2 4-hydroxylase. This enzyme is expressed primarily in extra-hepatic tissues (reviewed in Zhu and Conney, 1998, Martucci and Fishman, 1993).
>
> Specific information about the absorption, biotransformation and elimination of E2, E1 and 17α-oestradiol from meat and meat-product is not available. The effects of cooking and other processing on the bioavailability of such compounds is also lacking. Based on the lipophilicity of oestradiol, there is no reason to assume that such compounds will be poorly absorbed. Metabolic studies of orally administered 17ß-oestradiol indicate that as much as 20 percent of a 2 mg dose of micronized E2 is absorbed, with a serum half-life in the range of 2 to 16 hours (Zimmermann et al., 1998; Vree and Timmer, 1988: Ginsburg et al., 1998). In a 1998 study (Lippert et al., 1998) of oestradiol metabolism in postmenopausal woman orally administered oestradiol valeriate, 2 mg/day for 2 weeks, it was shown that along with the increased serum concentrations of oestradiol, there was a proportionate increase in the level of estrone, 2-hydroxyestrone and 16α-hydroxyestrone. Thus exposure to exogenous

> oestrogens leads to increased levels of the parent oestrogen compounds and their metabolites."

156. Moreover, as regards the young children – which is most vulnerable segment of the population - the 1999 opinion states (on pages 38-39) on this point the following:

> "However, there are two potential problems with these values. First, as mentioned previously (*Exposure Considerations Section)*, determination of plasma concentrations of oestradiol is subject to considerable variability, relative insensitivity given its low levels in children, and interference. A new, highly specific, more sensitive assay for oestradiol indicated that blood oestradiol levels in girls may be as much a 13 fold less and in boys 100 fold less than previous determinations using RIAs indicate. Second, it does not appear that MCRs have ever been determined directly in children. Rather, it appears as if MCR values from adult women were used in the calculations of the PRs for children (Andersson and Skakkebaek, 1999). This approach may or may not be valid given the known differences in levels of SHBG (higher in children, which would reduce clearance), and likely differences in uptake and metabolism, etc. Given these issues, it is possible that the safety margin for oestradiol exposure used by the FDA may be in error and that acceptable levels of hormone residues in beef could be much lower. (Similar concerns apply to progesterone and testosterone). The median level of excess exposure to oestradiol from consuming meat from hormone-treated cattle is 6.8 ng/person/day (calculated from Table A3, Annex, range 1 to 84 ng/person/day). For comparative purposes, assuming 100% absorption and a whole blood volume of 78ml/kg body weight, for a 40 kg child, based on the median value for excess oestrogen exposure, the blood concentration calculates to be 2.2 pg/ml (1 to 26 pg/ml). If the blood oestrogen levels are 100 fold lower than previously determined and the MCR too high by a factor of 10, the oestradiol daily production rate could be as low as 6 ng, and 1% of this would be 60pg. Thus, the FDAs acceptable daily intake (102 ng/person/day, see above) could exceed the daily production rate of oestradiol by 1,700 fold. While there is some experimental evidence in support of the currently used blood levels of oestradiol being 100 fold too high (Klein et al., 1994), the other assumptions used in coming to this conclusion may be too conservative. Thus, if absorption is reduced to 10% and the MCR for children is only 1/2 that of adults, the FDA acceptable daily intake could still be 85 fold too high. Given all of the uncertainties in these estimates, it appears that the data are insufficient to form the basis of a sound risk assessment. Clearly, this is an important area for additional research."

157. It has to be pointed out, however, that there is significant disagreement among scientists on the bioavailability of oestradiol in the specific oral pathway considered here, where the level of bioavailability cited in peer reviewed scientific literature ranges from 5% to 20%.

158. Moreover, similar finding are made for all the other five hormones. In addition, the 2002 opinion of the SCVPH further explained that the aim of one study (**study no 10 by Dr. Florence Le GAc**) was in particular to determine whether anabolics and their metabolites compete with natural sex hormones for binding to sex hormone binding globulin (SHBG / SBP). Theoretically, if this were indeed the case, tissues would be deprived of natural hormones that affect the development of sex hormone target organs during diverse stages of development. The data collected, shows a pattern of binding to SHBP and competition with ^{3}H-testosterone by ethynyl oestradiol, zearanolol alpha and beta, 19-nortestosterone, trenbolone acetate and 17β - trenbolone, and other natural androgens, not much different from those reported by others. The synthetic compounds did not bind to SHBG in blood plasma with high affinity. This study concluded that the lack of significant binding of zeranol

and its metabolites to SHBG suggest that when present in plasma their effect in brain and other oestrogen target organs is not neutralized by their weak binding to this plasma-borne protein.

159. Furthermore, the 2002 opinion considered (on page 12, section 4.1.5) the results of one more study (**the study no 3)** which found *inter alia* that:

> "The obtained results indicate that the potency of 17α-E2 is approximately 10% of 17β-E2. However, the potency of the lipoidal esters exceeded the effect of 17β-E2 in the in vivo assay by approximately a factor of 10 (Paris et al., 2001). Furthermore, lipoidal esters appear to have an even higher effect on the mammary gland in experimental animals (Mills et al., 2001). The high potency of lipoidal esters after oral applications might be explained by the fact that they reach systemic circulation via the lymphatic system, as suggested by preliminary data. These findings warrant further investigation, as a high bioavailability of biologically active lipoidal esters and the possibility of accumulation (Zarner et al., 1985) might contribute significantly to an undesirable exposure to oestrogenic substances. The impact of residual protein bound non-extractable oestrogen remains to be elucidated. In conclusion, it has to be stated that lipoidal esters of oestradiol add to the oestrogen exposure, as mentioned above. While the oral bioavailability of these metabolites was high in animal experiments, no information is available on the oral bioavailability in humans following dietary exposure via contaminated meat products."

Q29. Is the relatively low dose used for animal growth promotion purposes relevant for the risk assessment at issue? In what manner has this factor affected the result of the EC's risk assessment?

160. It should be clarified first that it is generally recognised that for substances which have genotoxic potential (as is the case with oestradiol 17β) the low dose used in animal growth promotion is not relevant, precisely because the possible genotoxic risks may arise at any dose. This being said, generally speaking, yes it is a relevant factor and the relative doses of hormones used for animal growth promotion purposes and the level of residues they give rise to in the different animal tissues has been taken into account in the European Communities' risk assessment. This is explained in detail for each of the six hormones in particular in the 1999 opinion of the SCVPH, which discusses this issue in several places. See, for example, table 2 on page 35 as regards oestradiol and the ensuing discussion; table 5 on page 47 as regards testosterone and the ensuing discussion; table 7 on page 52 as regards progesterone and the ensuing discussion; table 8 on page 56 as regards trenbolone acetate and the ensuing discussion; tables 10a and 10b on page 63 as regards zeranol and the ensuing discussion; and pages 66-68 as regards melengestrol acetate. As regards melegenstrol acetate, the 2002 opinion also analysed the more recent data resulting from the studies nos 5 and 10 (see section 4.5.2, pages 17-18 of the 2002 opinion).

161. The 1999 opinion concluded on this point that:

> "Endogenous hormones and their metabolites are present in measurable amounts in various animal tissues including meat (Section 3.1. and 4.1.5., 4.2.4., 4.3.4., 4.4.4., 4.5.4., 4.6.4.). The concentrations found, reflect different stages of the animals life cycle as exemplified by the high levels of testosterone in tissues of male cattle (bulls) or oestrogen and progesterone levels in tissues of young females (heifers) at a late stage of pregnancy (240 days gestation). Heifers are slaughtered and enter the food chain only exceptionally. It is therefore questionable whether levels in such animals should be included in estimates of the upper range of hormonal levels in meat and edible tissues. In contrast, for pharmaceutical products containing one or more of the

> three natural hormones, it is estimated that the use of these growth promoting agents will result in an additional excess daily intake of oestrogens in the range of 1 to 84 ng/person (17-β oestradiol + estrone), of progesterone of 64 to 467 ng/person, and of testosterone of 5 to 189 ng/person. As the levels of the synthetic compounds used as growth promoting agents are virtually zero in untreated animals, any residual amount in edible tissues must be regarded as excess exposure (see section 3.1). No validated data exists on the bioavailability of hormones and their metabolites after oral ingestion with meat."

Q30. Regarding the potential risks to consumers from the consumption of beef from cattle treated with testosterone, progesterone, zeranol, TBA and MGA, could the European Communities explain why, in the light of the available evidence, the European Communities has determined that the relevant scientific evidence is insufficient to permit the assessment of risks in a manner consistent with Article 5.1 and Annex A(4) of the *SPS Agreement*? With respect to what elements of risks does the European Communities believe that the available scientific evidence is insufficient?

162. As explained in the Recital 7 of Directive 2003/74 EC:

> "the SCVPH assessment [of 1999] is that, in spite of the individual toxicological and epidemiological data available, which were taken into account, the current state of knowledge does not make it possible to give a quantitative estimate of the risk to consumers."

163. This assessment has not been reversed by the new scientific evidence available after 1999 and later assessed by the SCVPH, as explained in the Recital 10 of the said Directive (see reply to question 19).

164. Specific assessments have been conducted regarding the potential risks to consumers from the consumption of beef from cattle treated with each of these five hormones for growth promotion purposes. These assessments have identified that, for each hormone, the level of information missing or contradictory was variable, at each individual step of the risk assessment.

165. The SCVPH has itself, in answering the questions of its mandate to perform the assessment of risks at stake, identified clearly where the information was felt insufficient. Question 1 (b) of SCVPH's mandate was formulated as follows:

> To what extent is the currently available information (clinical and epidemiological evidence included) sufficient to allow the SCVPH to complete its assessment, in particular for melengestrol acetate (MGA)?

166. In its reply, the SCVPH stated for all the six hormones the following:

> *ad 1 (b):* With the exception of 17-ß oestradiol, the currently available information for testosterone, progesterone and the synthetic hormones zeranol, trenbolone and particularly MGA has been considered inadequate to complete an assessment. This conclusion is based upon:
>
> – incomplete data on the biotranformation pathways of these compounds and the possible biological activity of the metabolites formed in bovine tissues as, for example, testosterone might be aromatized to oestradiol.

– lack of data on the potential genotoxicity of these metabolites in consideration of the current state of the art for genotoxicity testing as indicated in the answer to question 2 (a).

– insufficient data on immunological and immunotoxical effects.

Based on experimental and epidemiological data, testosterone and progesterone have been classified by IARC as Group 2 substances - probable/possible carcinogens in humans. No epidemiological data are available for zeranol, trenbolone and MGA (melengesterol acetate) although residues of hormonally active compounds in (poultry) meat have been shown to exert an oestrogenic response in prepubertal children in certain countries. **Thus, no final conclusions can be drawn with respect to the safety of at least five out of the six substances under consideration, until the above described issues have been clarified. For oestradiol genotoxicity has already been demonstrated explicitly.** (emphasis added)

Q31. The Panel is aware that the FAO/WHO *Codex Alimentarius* Commission has adopted standards with respect to five of the hormones at issue. For TBA and zeranol, the Codex has established MRLs; for oestradiol, testosterone and progesterone, the Codex decided that no MRLs were necessary. Please explain whether the European Communities believes that the Codex standards have been developed without "sufficient scientific evidence". With respect to what elements of risks do you believe that the available scientific evidence is insufficient?

167. For the reasons explained with its reply to question no 22, the European Communities considers that the standards adopted by the Codex Alimentarius Commission cannot achieve its chosen level of protection. The Codex Alimentarius standards are based on the assessments of JECFA mentioned above, which have suggested that it is unnecessary to set maximum residue limits (MRLs) for oestradiol 17ß, testosterone and progesterone because they considered that residues resulting from the use of these substances as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health and also because it is impossible to identify the real origin of any residues in meat (i.e. whether it is from endogenous production or exogenous administration), since the available detection methods are not capable of performing this kind of analysis. But for zeranol and trenbolone acetate MRLs have been proposed by JECFA.

168. However, as already explained the above-mentioned JECFA reports found that oestradiol 17ß "*has genotoxic potential*" and that the evidence for progesterone was interpreted "*on balance*" as not having genotoxic potential. On the basis of these findings, JECFA did consider for the first time that ADIs were necessary to be fixed but not MRLs, because of the endogenous production of these natural hormones and the difficulties in applying the available detection methods in order to determine the origin of any residues in meat. But the European Communities could not adopt the risk management options proposed by JECFA, because the scientific risk assessment of the SCVPH did not come to the same conclusions as those of JECFA (see the passages from the SCVPH opinion listed above). One of the difficulties of the JECFA reports, for instance, is that JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not. Therefore, after the examination of the full range of risk management options and taking into account the potential advantages and disadvantages as well as consequences and feasibility of risk management options (in particular that of control), the European Communities regulatory authorities concluded that the prohibition of the use of hormones for growth promotion within the European Communities and the exclusion of import of meat derived from animals treated with hormonal growth promoters was the most appropriate measure in order to protect its consumers from the risks identified from excess intake of hormone residues and their metabolites and the potential for abuse, *inter alia*, through non-observance of good husbandry practices. In other words, the European

Communities came to the conclusion that the JECFA's recommendations could not achieve the level of health protection considered appropriate by the European Communities in its territory from residues of these hormones under realistic conditions of use for animal growth promotion.

169. Moreover, the JECFA evaluations date of 1999 for the three natural hormones. It follows that they did not take into account the most recent data generated by the 17 studies initiated by the European Communities, upon which the three opinions of the SCVPH are also based. Consequently, it appears that the Codex Alimentarius standards have indeed been adopted on previous evidence, which by today's standards must be considered to be old. It is also generally accepted that evidence which is old becomes scientifically and legally "insufficient" when more recent information and data put into question its evidentiary value for the purposes of a risk assessment. Moreover, to the extent both JECFA and the relevant scientific committees of the European Communities considered partly the same evidence, they arrived at different results.

170. Finally, the elements of risks for which the JECFA assessment must be considered to be "insufficient" are explained, *inter alia*, with the reply to Question No 30 above.

171. Moreover, the European Communities has carried over a number of years several inspection mission in the USA and Canada in order to review and verify the respect of GVP and the extent of residue monitoring and control by the defending members. From these reports it is clear that there were a number of serious irregularities in the residue monitoring both in the USA and Canada (farm level as well as the laboratory testing itself). For instance, the results from the 2000 mission reports to USA and Canada can be found at the following website of the European Commission:

- http://europa.eu.int/comm/food/fs/inspections/vi/reports/usa/index_en.html.

and

- http://europa.eu.int/comm/food/fs/inspections/vi/reports/canada/index_en.html.

172. The above were further considerations that have led the responsible risk management authorities of the European Communities to conclude that under the realistic conditions of use, the standards recommended by Codex Alimentarius are not capable of achieving the chosen high level of protection by the European Communities from residues resulting from the consumption of meat from animals to which these hormones have been administered for growth promotion purposes.

Q32. Can the European Communities provide the Panel with a copy of the requests for information made to the United States, Canada and New Zealand in relation to scientific studies?

173. The European Communities will provide the Panel with the requested copies of these letters, which date back to April 1998. In fact, they have been archived in storage facilities outside the headquarters of the European Commission and are therefore difficult to retrieve. The European Communities apologizes for the delay. It will submit the copies as soon as it has retrieved them from the archives.

Q33. With respect to the written request made by the United States to the European Communities under Article 5.8 of the *SPS Agreement* for an explanation on the consistency of the EC's implementing measure, could the European Communities provide the Panel with a copy of its written response of 19 May 2005 (US first written submission, para. 194)? Could the EC explain why it replied to the US request for information pursuant to Article 5.8 of the *SPS Agreement* only after having requested the establishment of a panel?

174. The European Communities provides its written responses to the United States request under Article 5.8 of the *SPS Agreement* as Exhibit EC-7 (US) and Exhibit EC-5 (CAN)

175. Regarding the second part of the question, the United States, after not requesting anything for one and a half year since the notification of the new Directive to the WTO, or even having not commented to any of the earlier European Communities' calls for scientific input in its risk assessment, sent this request some time after the European Communities requested consultations in the present case: its request came on 13 December 2004, at the same time the consultations under these proceedings were held (16 December), which means more than one month after these consultations were requested by the EC.

176. It is a fact, therefore, that the United States' request came after these proceedings have started by the European Communities. The European Communities believes that the United States' request was in fact stemmed by our request for consultations, when they realised that the European Communities was serious about this issue and would certainly request the establishment of a Panel, as they had already then no intention to suspend their sanctions against us.

177. Their request was, therefore, part of the preparation of their defence strategy in this case, namely that they are now claiming to still "consider" our measure to comply, despite the many bilateral exchanges and requests for information which they had systematically denied before.

178. The exact date of the United States' request was 13 December 2004 and the European Communities requested the establishment of this Panel in 13 January 2005. With the standard administrative procedure to handle such requests, the European Communities took approximately 5 months to reply to the United States' request on 19 May 2005, a perfectly reasonable period of time, which should not come as a surprise, in the light of the internal institutional consultations required within the European Communities on issues of such a nature, and taking into account that Christmas and Eastern breaks had intervened in the meantime.

179. It would certainly be absurd to assume that such a reply could have been ready right after the Christmas break, before the request to establish the Panel, which had to follow naturally in the light of the lack of willingness of the United States to consider interrupting their sanctions in the preceding consultations.

180. Nevertheless, already at the time of its notification according to the *SPS Agreement*, the new Directive, and the risk assessments requested by the United States and which are provided for by the opinions of the SCVPH, were all publicly available through internet, as well as the scientific studies on which these assessments were based.

181. Finally, the European Communities would note that Canada never made any similar request under Article 5.8 of the *SPS Agreement*.

Q34. With reference to the EC statement in paragraph 102 of the EC's oral presentation that the European Communities "would have lifted the ban for these hormones if their use for growth promotion purposes were proven to be safe for the public health and would have met its chosen level of protection", please explain how the *safety* of the hormones could be proven?

182. The safety would have to be proven to the requisite legal standard by a state-of-the-art risk assessment taking into account the latest scientific information and data available. More importantly, the information and data gaps identified in the recent risk assessments and in particular those identified in the three opinions of the SCVPH would have to be clarified and properly addressed. This would require a lot of new information to be brought forward on all the crucial questions identified in the 1999 SCVPH opinion. It would in particular have to be shown that human exposure to residues of

hormonally-active substances contained in growth promoters used for meat production does not exert or has not the potential of exerting the harmful biological effects identified in the 1999 SCVPH opinion (e.g. cancer, on prepubertal children, etc.). This assessment would have to be performed on the basis of real situations of use, if authorised, so as to avoid the potential problems of misuse or abuse in order to achieve the high level of protection of no additional risk from the residues in meat of animals to which these hormones have been administered for growth promotion purposes. For instance, a group of independent USA scientists has recently published in a peer reviewed scientific journal that:

> "Zeranol (Ralgro) is a nonsteroidal agent with estrogenic activity that is used as a growth promoter in the US beef and veal industry. Thus zeranol is not an environmental contaminant per se. Rather, people are exposed to zeranol as a result of introduction of the compound into food animals by veterinary professionals on behalf of beef industry farmers. We have shown that meat and serum from zeranol-implanted cattle possess heat-stable mitogenicity for cultured breast cells, and that both normal and cancerous human breast cells exhibit estrogenic responses to zeranol (6-8). Evidence indicates potential tumorigenic mechanisms for estrogen, such as direct genotoxic effects of estrogen metabolites and estrogen-induced expression of genes encoding growth and transcription factors. However, despite the clear importance of estrogens in the etiology of breast cancer, the mechanisms responsible for estrogenstimulated carcinogenesis remain undefined."[42]

183. The research for this study was supported by Ohio State University, the US National Cancer Institute and the US Department of Defence Breast Cancer Research program. This paper is appended as Exhibit EC-6 (US) and EC-8 (CAN). The European Communities would expect that the USA competent authorities will take the necessary steps to try and clarify the issues raised in this study and that other cautious WTO members would be entitled to take into account this kind of evidence, and many more which the European Communities will provide with its rebuttal, when assessing the safety of these substances.

[Questions 35 through 49 – Questions to US and Canada]

Q50. Could each party provide the Panel with a detailed account of the efforts it has made to solve this dispute since the notification by the European Communities of its implementing measure in 2003?

184. The European Communities undertook repeated efforts with the United States and Canada with the aim of agreeing on a procedure through which the existing disagreement over compliance could be resolved in accordance with the DSU, i.e. multilaterally. To this effect, discussions were held at the technical level from fall 2003 on the following possibilities: (i) a compliance review under Article 21.5 of the DSU, possibly with agreed terms of reference, or (ii) an agreed arbitration under Article 25 of the DSU, also with agreed terms of reference. The European Communities also made clear that, in the absence of the United States' and Canada's action according to options (i) or (ii), it would have no other choice than to launch an independent dispute against the continuation of the United States' and Canadian suspension of obligations. These discussions continued at the technical level into the beginning of the year 2004 and covered specific aspects of the terms of reference that could be agreed, in particular for an arbitration under Article 25 of the DSU.

[42] Suling Liu, and Young C. Lin: Transformation of MCF-10A Human Breast Epithelial Cells by Zeranol and Estradiol-1 7ß, *The Breast Journal, Volume 10, Number 6, 2004 514-521 (*2004). Exhibit EC-8 (US), 6 (CAN).

185. In January and February 2004, the issue of an agreed procedure for the review of the new Hormones Directive's WTO-compliance was also on the agenda of several meetings and phone calls which Commissioner Pascal Lamy had with Trade Representative Robert Zoellick and with Minister Jim Peterson. The last contact at ministerial level was a discussion between Commissioner Pascal Lamy and Ambassador Robert Zoellick in October 2004 shortly after the adoption by Congress of the American Jobs Creation Act of 2004. Mr. Lamy conveyed the European Communities' intention to initiate a procedure under Article 21.5 of the DSU against the WTO-inconsistent implementation in *US – FSC*. He also indicated the intention to propose to the Council of the European Union that the European Communities' countermeasures against the United States in *FSC* be suspended during the Article 21.5 review. He added that the European Communities expected the United States to proceed in the same manner as regards its suspension of obligations in *EC – Hormones*. Unfortunately, all these efforts have not borne fruit. In the absence of a positive reply, the European Communities decided to initiate the present dispute against the United States' and Canada's ongoing suspension of obligations. During the consultations in this dispute, the European Communities reiterated to the United States and Canada its offer not to pursue this case if the United States and Canada suspended their sanctions and initiated Article 21.5 proceedings.

Q51. Having regard to the first claim of the European Communities, in a post-retaliation phase, if a suspension of concessions is consistent with Article 22.8, can it nevertheless be inconsistent with Article 23 of the DSU? Under what circumstances? Please elaborate.

186. Yes, it can be inconsistent with Article 23 while being consistent with Article 22.8. The difference lies in who determines whether the measure has been "removed" within the meaning of Article 22.8. A Member who unilaterally determines that the inconsistency of the measure has not been removed and continues to apply sanctions on that basis, is in violation of Article 23, even if later it is multilaterally established that the measure had indeed not been removed and, therefore, that there is no violation of Article 22.8. The European Communities refers also to its answer to Question 13.

Q52. In the *US – FSC* case, the European Communities suspended the application of its suspension of concessions and then initiated an Article 21.5 procedure because it considered that the US implementing legislation was inconsistent, *inter alia*, with the SCM Agreement. Please give your views on whether it would also be possible to request the establishment of an Article 21.5 panel while continuing to apply the suspension of concessions pending the outcome of the Article 21.5 procedure?

187. The European Communities understands this question to inquire whether the suspension of concessions may continue while an Article 21.5 procedure is ongoing. In the European Communities' view there is no need for the Panel to give a general response to this question in the present proceeding. In the present case, the United States and Canada have violated Article 23 read together with Article 21.5 because they failed to initiate a compliance review for nearly one and a half years when this panel was established while continuing to apply sanctions. Accordingly, if the Panel agrees with this proposition, the United States and Canada will have to end their sanctions once the DSB has adopted the recommendations and rulings in this case. They cannot then initiate a compliance review and maintain the sanctions because this would defy the logic of the finding of a violation that consists of the application of sanctions and the non-initiation of the compliance review over a protracted period of time. Under these circumstances, there is no need to decide on the principle of whether the sanctions must be lifted (suspended) in a different case, where the original complainant initiates an Article 21.5 procedure in a timely fashion.

Q53. Are the parties of the view that, in the absence of a challenge by the implementing party against the continued suspension of concessions, such suspension can continue for an indefinite period of time, even though they are supposed to be only temporary. If not, what provision of

the DSU can serve as a legal basis for *preventing* the suspension of concessions for an indefinite period of time?

188. In the European Communities' view, where an implementing measure has been adopted, Members are prevented from suspending concessions for an indefinite period of time through Article 23 in conjunction with Article 22.8. These provisions read together require Members to challenge another Member's implementing measure if they consider it to be WTO inconsistent and thus prohibits them to simply continue to apply sanctions.

189. By contrast, while it is true that the suspension of concessions, according to Article 22.8 is only temporary, a Member would not be prevented from continuing to suspend concessions for an indefinite period of time in the absence of any implementing measure, i.e. where another Member would simply refuse to remove the measure that has been found to be inconsistent with a covered agreement.

Q54. Could the parties provide the Panel with their understanding of the meaning of the term "measure" in Article 19.1 of the DSU and of the term "measures taken to comply with the recommendations and rulings [of the DSB]" in Article 21.5 of the DSU? More particularly, do the parties consider that a measure taking, e.g., the form of a ban remains the same measure, irrespective of the change in supporting legislation, as long as it is a ban? If not, what makes a "measure taken to comply" different from the measure which had to be brought into conformity?

190. The "measure" within the meaning of Article 19.1 of the DSU is the measure that has been found to be inconsistent with a covered agreement. The findings identify the reasons for the inconsistency. The recommendation to bring the measure into conformity, in turn, must be read in light of these findings.

191. The "measure taken to comply" within the meaning of Article 21.5 of the DSU, is the measure that has been (or should be) taken to bring about compliance with the above recommendation.[43] Compliance depends on the reasons for inconsistency as they have been identified in the findings.

192. How to distinguish the two measures is a question that can be asked on two levels: on a formal/procedural level (has a Member adopted a new measure in order to bring about compliance?) and on a substantive level (has the Member actually achieved compliance?). The assessment on the latter level is clearly the task of a compliance panel.

193. In the present case, a new measure has been adopted to bring about compliance (a new Directive adopted by the Council and the European Parliament). Formally, therefore, there is a measure distinct from the original measure. Whether that measure is distinct also on a level of substance is a question of what compliance is about in this case. The reasons of inconsistency of the old *Hormones* legislation have been identified by the Panel and Appellate Body in their respective findings. They all relate to the risk assessment underlying the import prohibition. That risk assessment was essentially found not to sufficiently warrant a measure consisting in an import prohibition. Thus, it was not an import prohibition *as such*, that was found to be inconsistent with the *SPS Agreement*, but the particular import prohibition as based on the (deficient) risk assessment in question.

194. The new measure addresses these reasons for inconsistency in that it is based on a new risk assessment. The new risk assessment fully warrants a (definitive) import prohibition on one hormonal

[43] *See* also Appellate Body Report, *Canada – Aircraft (21.5 – Brazil)*, at para. 36.

substance in question and yields enough available pertinent information to support a provisional import prohibition on the other five substances. Therefore, also on the level of substance, the measure taken to comply is a different one from the original measure found to be inconsistent irrespective of the fact that, in form, it remains an import prohibition.[44]

Q55. When does the legal effect of the DSB authorization lapse and by what procedures? Where parties disagree on the consistency of a notified implementing measure effected after the DSU retaliation authorization, does the DSU authorization lapse at the time when (i) the DSB makes a decision of compliance with respect to the implementing measure, or (ii) the implementing measure is in actual compliance regardless of whether the DSB has made a determination of compliance or not, or (iii) the Member concerned notifies its implementing measure to the DSB and declares its compliance, or (iv) the DSB makes a specific determination to terminate its previous retaliation authorization?

195. The European Communities expresses no view as regards whether and when the DSB authorization "lapses" in the sense of "ceases to exist". Where the European Communities has a clear view is the question of until when the suspension of obligations may be "applied".

196. As regards the possible answers which the Panel is presenting in this question, one has to distinguish: The answer is (ii) under Article 22.8 of the DSU, i.e. when the implementing measure is in actual compliance regardless of whether the DSB has made a determination of compliance or not. The reason is that Article 22.8 contains an obligation to cease the suspension of concessions if the measure has been removed. That obligation directly applies to the Member imposing retaliation. The DSB authorization cannot overrule this obligation. To the contrary, its legal effects are dependent on it. That is why a Member is no longer entitled to suspend obligations if the conditions of Article 22.8 are fulfilled.

197. Under Article 23 in conjunction with Article 22.8, however, a Member is not entitled to continue the suspension of obligations if this is based on a unilateral determination and accompanied by the failure to have recourse to the rules and procedures of the DSU.

Q56. Article 21.5 of the DSU provides that where there is a "*disagreement* as to the existence or consistency with a covered agreement of measures taken to comply with ... such dispute shall be decided through recourse to these dispute settlement procedures." Since Article 21.5 provides that "such dispute *shall* be decided"[45] through recourse to [the DSU]", would the parties consider that either of them has an obligation to refer the matter to the DSB under Article 21.5? If yes, why?

198. In the European Communities' view the "shall" refers to the obligation to resort to the dispute settlement procedures under the DSU, and more particularly to the one under Article 21.5, *if and when* it is envisaged to seek redress because of a disagreement on compliance. By contrast, it does not imply an obligation to *initiate* such a dispute in the absence of any desire to take action based on a

[44] *See* also the case *Japan – Apples* where the implementing measure maintained elements of the original measure. The Panel, in the case, found: "In its implementation process, Japan has made some changes to the original measure [footnote omitted] and has produced new studies to support its view that (a) mature, symptomless apples can be "latently" infected and (b) infected apples could, once on the Japanese territory, contaminate host plants. On the basis of these studies, Japan has maintained many elements of the original measure in the measure taken to comply. For this reason, we consider that all the elements of the measure currently in place should be treated as the "measures taken to comply", even though many of those elements were already found in the original measure [footnote omitted], *See* Panel report *Japan – Apples (21.5)*, at para. 8.32.

[45] Emphasis added by the Panel.

belief that there is non compliance. Article 21.5 makes clear ("shall be decided") that Members are not entitled to decide such disagreements through other means, as the United States and Canada have done by unilaterally deciding that there is no compliance and thus continuing their sanctions. This is confirmed by Article 23.

Q57. How would you distinguish between expressing "disagreement" over the WTO compatibility of a measure taken to comply with recommendations and rulings adopted by the DSB for the purpose of deciding whether or not to start an Article 21.5 procedure and a unilateral "determination" of WTO compatibility of such a measure?

199. The "disagreement" is less than a "determination." If a Member has made a determination within the meaning of Article 23.2(a) that there is no compliance, this will imply that there exists also a disagreement within the meaning of Article 21.5 (unless, of course, the original respondent agrees that there is no compliance). On the other hand, such a disagreement may exist without a Member having yet made a determination. The difference is that a determination is linked to the action of seeking redress implying that a Member takes steps to address what it perceives to be a case of non compliance. A disagreement, by contrast, does not (necessarily) imply taking any steps.

200. To illustrate the difference: If the defending parties had suspended the application of retaliatory measures, but had otherwise reacted in the same way as they have, i.e. making statements to the effect that they fail to see how the new measure could be compliant etc., there would be a disagreement, but no determination.

Q58. In a situation where an Article 21.5 panel, requested to examine the compatibility of an implementing measure, finds that only partial compliance has been achieved, what is the procedure available to the original complainant: (a) Can it continue to apply the suspension of concessions initially authorized by the DSB?; (b) Does it need to request a new authorization?(c) Can the implementing party object to the level of suspension and request an Article 22.6 arbitration to determine a new level of suspension of concessions?

201. If a 21.5 panel is called upon to rule on nullification and impairment it can rule that the level is less following partial implementation. Furthermore, the European Communities notes that in the case *US – FSC (second Article 21.5)* (report not adopted yet) the panel was confronted with partial compliance and opined that

> Although the phased reduction in amount of subsidy available in 2005 and 2006 may be relevant in another type of proceeding, such as an arbitration under Article 22.6 of the DSU or Article 4.10 and 4.11 of the SCM Agreement, the fact that, in 2005 and 2006, the percentage of subsidy available is less than the entire amount that was available under the ETI Act before 2005 is not material to our inquiry under the Article 21.5 DSU proceeding. 46

202. Thus, that panel seems to imply that an arbitration procedure under Article 22.6 would be possible. It is unclear, whether the Panel was suggesting that a new request for an authorization is required and whether there could be a suspension of concessions pending the outcome of the arbitration procedure. The European Communities is still considering the correctness of this statement and its implications, which may be subject to review by the Appellate Body.

[46] Panel Report, *US – FSC (second Article 21.5)*, not yet adopted, at para. 7.60, Footnote 78.

Q59. Is Article 23 of the DSU applicable to a suspension of concessions under a previous authorization of the DSB and in the absence of a new DSB decision of termination of the previous authorization?

203. Yes, Article 23 is applicable to such a situation, since it applies always when Members are "seeking redress". Indeed, it is difficult to see why it would not be applicable, i.e. which condition of its application would be lacking. The defending parties pretend that the element "seeking redress of a violation" is missing, because they would already have "sought and obtained" redress under the previous authorization.[47] In the European Communities' view this statement not only relies on a different meaning of the word "to seek" – one which does not make sense in the context of Article 23[48] – but it also lacks logic as the defending parties themselves admit that suspending concessions is a form of seeking redress.[49]

204. Also, the European Communities would reiterate that both legally and practically speaking there is, under the present rules, no such thing as a "new DSB decision of termination of the previous authorization".

Q60. Having regard to the US reference to the DSU negotiations in footnote 202 of its first written submission, could the parties indicate which proposals have been made in that context that would represent *amendments* to the current text of Articles 21.5, 22.8, 23.1 and 23.2(a) of the DSU?

205. As the European Communities has pointed out, this Panel is asked to interpret and clarify, in accordance with its mandate under the DSU, the existing provisions of that understanding. The fact that related questions are under discussions in the negotiations on improvements and clarifications of the DSU and whether or not there is consensus among Members on how the rules should be improved in that regard is therefore without direct relevance to this dispute. The Panel must apply the existing procedural rules of the DSU to this case, and the rights and obligations of Members under the existing rules cannot be altered by whatever Members may be discussing in the special session of the DSB as regards future DSU rules – whether improved or merely clarified.

206. Given that the Panel has stressed "amendments" in its question, the European Communities would once more point out that what does not exist in the current DSU rules is an explicit and streamlined mechanism for a formal removal of a previously granted DSB authorization to suspend obligations. Such a mechanism has indeed been the subject of the negotiations on a review of the DSU. The present absence of such a formal mechanism, however, in no way implies nor can the European Communities accept (contrary to the United States' stated belief at the first substantive meeting), that the current DSU rules contain no rules that regulate until what point a Member may suspend obligations pursuant to a once obtained DSB authorization. Also, there is no gap in the present rules since Article 21.5 of the DSU can serve to resolve a disagreement over compliance, which presupposes the complainant's initiative. Further, if like in the present case, the original complainant refuses to initiate a compliance review, the Member facing the suspension of obligations can challenge the legality of these sanctions in an ordinary panel procedure, as it has been done in the

[47] US First Written Submission, para. 175 ; Canada, First Written Submission, para. 68.

[48] There are the meanings of "seek" which have been identified by previous panels (*US – Certain* EC *Products*, at para 6.22) and which are "to resort to…to make an attempt, to try" (meanings which also the US identified, *see* US First Written Submission, at para. 172); and there is the other meaning which is "to ask for, to demand, to request" which is the one replied upon in the statement "sought and obtained" and authorization.

[49] Note also, and as pointed out in the EC First Written Submission, the Panel in *US – Certain* EC *Products* also found that suspension concessions (in order to seek redress of a violation) necessarily implies a determination, *see* Panel Report, *US – Certain* EC *Products*, at para. 6.100; *see* also EC First Written Submission, at para. 59.

present case. This is a long and complex recourse, but a possible one and the Panel may not refuse a ruling on this matter, lest a gap should be *created* in the current DSU and rights and obligations of Members diminished.

207. Ever since the DSU negotiations have started, the question of adding a more streamlined mechanism to bring sanctions to an end, notably by formally removing a previously granted DSB authorization to suspend obligations, has been on the table. Notably, in November 1999, several Members[50] co-sponsored a proposed amendment, the so-called Suzuki Text, which provided for such a specific remedy (WT/MIN(99)/8). The same proposed amendment was also contained in an amendment proposal of October 2001.[51] The Chairman's text of 2003 (which is 17 pages long, see TN/DS/9, and to this date the most recent draft text of proposed amendments authored by a Chairman of the DSB special session), maintained this remedy. It provides in essence that it is for the original complainant to challenge the WTO compatibility of the implementing measure, and if it does not do so within a specified time-period, the DSB formally withdraws the authorization by negative consensus. The start of that deadline is triggered through the implementing Member's qualified notification of its measure taken to comply. If a compliance review takes place and results in no findings of inconsistency, the DSB also withdraws the authorization to suspend obligations. If there is no full implementation, a new arbitration on the level of nullification or impairment may be requested and the DSB would subsequently modify the previous authorization accordingly.

208. It is worth recalling that the Chairman's text of May 2003 included only a select number of proposed elements of possible improvements and clarifications of the DSU. The Chairman's criterion for that selection was the degree of consensus among WTO Members in those negotiations.[52] Thus, while the Chairman's text was based on proposals made by individual or groups of Members, it omitted a large number of such proposals in view of the insufficient support which these had attracted in the course of the negotiations.[53] This is also evidenced in the Chairman's report of 6 June 2003 to the Trade Negotiations Committee: "A number of other proposals by Members could not be included in the Chair's proposal in the absence of a sufficiently high level of support, including, *inter alia*, …"[54] In some cases, the Chairman's text contained proposed amendments in square brackets to indicate a lower degree of consensus on the issue in question. It is worth noting that the proposed Article 22.9 of the DSU was part of the Chairman's text without square brackets.

209. In May 2004, Canada, who had been among the co-sponsors of the Suzuki Text, changed direction and, together with Argentina, Brazil, India, New Zealand and Norway, most of which are also third parties in this dispute, made a proposal under which it is solely for the original respondent to launch the compliance review in the post-retaliation phase (JOB(04)/52). The proposal specifies that the original complainant can submit new claims of violation after the original respondent has requested the establishment of the compliance panel and that the panel's terms of reference cover these as well. Listening to Canada at the first substantive meeting, the European Communities had the impression that Canada confuses the current rules with the procedures it has proposed to create. The joint proposal of Argentina, Brazil, Canada, India, New Zealand and Norway was substantially discussed in the special session of the DSB, where [confidential] that, despite the proposed initiation

[50] Canada, Costa Rica, Czech Republic, Ecuador, the European Communities and its member States, Hungary, Japan, Korea, New Zealand, Norway, Peru, Slovenia, Switzerland, Thailand and Venezuela.

[51] By Bolivia, Canada, Chile, Colombia, Costa Rica, Ecuador, Japan, Korea, New Zealand, Norway, Peru, Switzerland, Uruguay and Venezuela.

[52] See TN/DS/M/12, para. 1: "The Chairman said that the draft text reflected proposals on which there was a high level of convergence among Members."

[53] The totality of the draft text proposals submitted in those negotiations has been collected in a Compilation, *see* JOB(03)/10/Rev.3 and JOB(03)/10/Rev.4 (the version of spring 2003 and equally the further revision of October 2004 are each 102 pages long).

[54] TN/DS/9, page 1, para. 6.

of the compliance review by the original respondent, the respondent would not bear the burden of proof for its WTO compliance, given that established WTO jurisprudence makes clear that the party which asserts the *affirmative* of a claim or defence, not the *negative* thereof, bears the burden of proof.

210. Based on the discussion that had taken place in the special session of the DSB, the European Communities and Japan submitted an alternative text in March 2005 (JOB(05)/47). This proposal maintained (and further refined) the approach contained in the above-mentioned Chairman's text of May 2003 and thus also preserves the basic structure of WTO dispute settlement, namely that it is for complainants to initiate WTO disputes and to request the establishment of panels pursuant to Article 21.5 in conjunction with Article 6 of the DSU. That proposal was well received by a large number of Members, but some technical work remains and also the gap between the two recent texts in question.

211. Finally, the European Communities would like to point to an interesting proposal on dispute settlement which Canada has submitted in the negotiations on rules.[55] In that proposal, Canada proposes that an implementation measure would be considered WTO-compliant after a declaration of compliance to the DSB by the implementing Member and without the initiation of Article 21.5 proceedings within a prescribed period of time that is sufficient for the complaining Member to assess the adequacy of the compliance action (e.g. 60 days). Despite the different context (anti-dumping and countervailing duty enforcement action), the contrast between the position expressed in that proposal and Canada's position in the present dispute is quite striking.

Q61. How does the principle of good faith affect the allocation of burden of proof in these two disputes? What kind of presumption should be made by the Panel if/when applying this principle? Does the application of this principle under the circumstances of the present disputes lead to the conclusion that the EC's implementing measure shall not be presumed WTO-inconsistent? Or, should the conclusion be that the US and Canadian measures of suspension of obligations shall not be presumed to be inconsistent with the DSU? Please elaborate on why one specific conclusion is preferable than the other in your view.

212. It seems important to recall what the principle of good faith is about: To paraphrase the Appellate Body, the principle of good faith controls the exercise of rights [and the fulfilment of obligations][56] by states.[57] WTO Members are required to exercise their rights and comply with their obligations in good faith.[58] The principle of good faith has a number of "applications" (Appellate Body, *US – Shrimp*), which prohibit or prescribe a certain conduct on States (example of *US – Shrimp*: doctrine of *abus de droit*). Thus, the *principle* of good faith is about certain obligations of conduct that WTO Members have as contracting parties of the WTO agreements.[59]

213. The debate in the present case is about the *presumption* of good faith, which can be seen to be derived from the *principle* of good faith. Thus, it is not the obligation to act in good faith, but the presumption that that obligation has not been breached, which is of relevance in this case. That presumption, in turn, is but one aspect of the more general presumption that Members are acting in a manner consistent with their obligations under the WTO agreements.

[55] TN/RL/GEN/37 and [confidential].

[56] The Appellate Body, in the specific context of the case *US – Shrimp*, was discussing a right, namely the right to rely on the exception of Article XX of the GATT. Other case law shows clearly that the principle applies equally to the fulfilment of obligations, *see* for example *US – FSC*, Report of the Appellate Body, at para. 66.

[57] Appellate Body Report, *US – Shrimp*, at para. 158.

[58] For the DSU this is explicitly stated in Article 3.10.

[59] *See* also Article 26 of the Vienna Convention.

214. The presumption that Members are acting in a manner consistent with their obligations under the WTO agreements is the very basis of the dispute settlement system (as it is essentially for any dispute settlement or court system that is there to solve disputes about contractual obligations). Disputes are brought to establish that a Member has acted in a manner inconsistent with its WTO obligations. In bringing the case and making the assertion that there is a violation the presumption of compliance is rebutted. It is then, in turn, for the defending party to rebut the assertion. The burden of proof rules flow naturally from this logic.

215. On the basis of that logic the European Communities has brought the present cases in order to have established that the United States and Canada are acting in a manner inconsistent with their obligations (under the DSU). In accordance with the burden of proof rules the European Communities has made a *prima facie* case that there is a violation and the defending parties have come back with arguments to rebut that assertion. Had the European Communities (or anybody else) not brought any case against the defending parties, they would have had to be presumed to be acting consistently with their WTO obligations. Neither the European Communities nor anybody else would have the right to claim otherwise, by, for example applying retaliation (Article 23).[60]

216. The same logic should apply, in turn, to the European Communities' implementing measure in the *Hormones* dispute. In order to rebut the presumption that the European Communities, in adopting that measure, has acted in a manner consistent with its WTO obligations, the defending parties have to bring a case. The normal burden of proof rules would apply. The fact that they have precisely not brought such a case is (1) the reason why the European Communities is claiming that there is a violation of Article 23.1, 23.2(a) in conjunction with 21.5 and (2) the reason why the European Communities relies on the presumption of compliance in the context of its claim under Article 23 in conjunction with Article 22.8.

Q62. Do you agree with the view that (i) if an original complaining party initiates an Article 21.5 dispute challenging the consistency of an implementing measure, that party shall bear the burden to prove that the implementing measure is WTO-inconsistent during the compliance procedure, and that (ii) if an original defending party initiates an Article 21.5 dispute claiming the WTO-consistency of its measure, that original defending party shall bear the burden of establishing the consistency of its implementing measure as a complaining party to the Article 21.5 dispute? Please elaborate on your response.

217. The question illustrates well the systemic incoherencies that arise in bringing a case against oneself in order to establish that there is compliance.

218. Scenario (i) is the standard scenario, to which the burden of proof rules apply without any problem. Indeed, the (original) complaining parties would have the burden of proving that the implementing measure is WTO-inconsistent.

219. Scenario (ii), on the other hand, is no standard scenario. The following remarks apply to this case: Burden of proof rules do not depend on a particular procedural constellation, i.e. on who is the complaining and who is the defending party, but on who asserts the affirmative of a particular claim or defence.[61] Therefore, even in the role of the "defending party" in a 21.5 procedure initiated by the implementing Member, it is the original complaining party that would assert – and therefore have to prove – that there is WTO inconsistency. This much seems implied in the above question.

220. The difficulty lies in the assumption that, when initiating a case itself, the implementing Member would have to assert – and therefore prove – that there is WTO consistency. The above

[60] *See* also EC reply to Question 4.
[61] Appellate Body Report, *US – Wool Shirts and Blouses*, p. 16

burden of proof rules do not envisage such a case as they apply either to violation claims or to defences (i.e. claims of inconsistency or rebuttals to such claims), but not to a free-standing assertion that there is WTO consistency. The assertion that "there is WTO-consistency" is not a claim in the sense of DSU and not a basis for a dispute under Article 1.1 of the DSU, Article 11.1 of the *SPS Agreement* and Article XXIII of the GATT. Indeed, to the extent such an assertion would be about establishing that there is no violation of a WTO provision, a Member would have to assert, not the *affirmative*, but the *negative* of a claim (e.g. "no violation of Article 5.1"). This, however, is impossible, both in scope and substance: First in scope, because it would effectively mean going through every single provision of the WTO agreements in order to rule out any possible violation (compliance under Article 21.5, after all, means "consistency with *a* (i.e. <u>any</u>) covered agreement."). Second, in substance, because it would require anticipating what the possible problem could be under any particular provision.

221. The very case of the *Hormones* Directive demonstrates this impossibility. Not only is it impossible for the European Communities to rule out any possible violation there might be under the covered agreements, but it is even impossible to do so with regard to the specific violations that had been found by the DSB to exist under the old measure. Take the case of Article 5.1 of the *SPS Agreement*. The Appellate Body had found that the risk assessment presented by the European Communities at the time did not sufficiently warrant the prohibition laid down in the legislation. While it might still be conceivable to address the specific reasons why this had been the case at the time (e.g. specificity of the evidence relating to hormones generally but not to hormone residues in meat consumed by humans and arising from use for growth promotion purposes), it is virtually excluded to address all other possible reasons why the new risk assessment may not sufficiently warrant the new measure. Indeed, Canada and the United States might find a multitude of other reasons why the risk assessment might be flawed according to their belief. Thus, they might contest the methodology used, disagree with the results obtained, dismiss the quality of the scientists employed, reject the conclusions drawn etc. Such potential criticisms cannot be anticipated. What's more, putting the burden of anticipating them on the implementing Member would effectively lift the burden of the original complaining parties to assert and demonstrate inconsistency.

222. One could think of solving such problems by "tailoring" the burden of proving consistency to something "feasible" (no new violations? only those identified by rulings and recommendations? only those reasons identified by Appellate Body?). However, assuming for the moment that this were legally conceivable, which it is not, the burden of proof issue would then become even more of a moving target (opening up a battlefield of arguments of what is new/old) creating further procedural complexities.

223. These issues demonstrate well that it is against the very nature of the dispute settlement and its rules of burden of proof to assume that there exists a burden of proving consistency if such a burden is supposed to consist in anything else but the mere presentation of the implementing measure.

Q63. Would the parties consider that the principle *rebus sic stantibus*, could apply to a decision of the DSB (see, *inter alia*, para. 26 of Canada's oral presentation regarding the legal status of DSB decisions)? In its oral comments on Canada's oral presentation, the EC stated that there is no hierarchy in customary international law, the principle of good faith in this case, and a treaty language, the DSB authorization in the current dispute. Could the parties provide evidence that the EC statement is or is not supported by international jurisprudence?

224. This question requires first of all a few general remarks about the relationship between WTO agreements and customary international law (or other sources of international law).

225. As stated at the substantive meeting, a concept of hierarchy of norms comparable to what exists in domestic law does not exist in public international law. As the International Law Commission pointed out most recently, such a "concept [of hierarchy] […] was not present on the international legal plane and should not be superimposed."[62]

226. There are, however, different sources of public international law and these are enumerated in Article 38 of the ICJ Statute. As explained by *Brownlie*

> They are not stated to represent a hierarchy, but the draftsmen intended to give an *order* […].[63]

227. The reason for applying this order is essentially one of *specificity*, treaty law normally being of a more specific nature than customary law and general principles. [64] However, as *Lauterpacht*, points out

> […] the order of the sources of international law as thus indicated cannot be applied in a mechanical way. Nor does it fully express their relative importance. Undoubtedly, the rights and duties of States must be determined in the first instance by reference to applicable treaties. Yet, while it is true that international customary law applies only in the absence of available provisions of treaties, and that 'general principles of law' are merely a residuary source of law in cases in which there is no applicable treaty or custom, treaties, in turn, must be interpreted in the light of customary international law [footnote omitted] - just, as the latter, as well as treaties, must be interpreted against the background of general principles of law. When the meaning of a treaty is not clear, it must be assumed that the parties intended it to be in conformity with general customary, international law – and it is then that customary international law becomes relevant and decisive, notwithstanding any hierarchical order establishing the priority of a treaty.[65]

228. The panel in the case *Korea – Government Procurement* accurately applied these concepts to the issue of the relationship between the WTO agreements and customary international law, when stating that

> Customary international law applies generally to the economic relations between the WTO Members. Such international law applies to the extent that the WTO treaty agreements do not "contract out" from it. To put it another way, to the extent there is

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[62] 2002 ILC Report, at p. 506. *See* also, for example, *Knut Ipsen*, Völkerrecht, 3. Auflage, at p.222, para. 1 : "Die Lösung [von] Konfliktfälle[n] [zwischen Normen die verschiedenen Rechtsquellen angehören] bereitet Schwierigkeiten, weil dem Völkerrecht eine dem innerstaatlichen Recht vergleichbare Normenhierarchie fremd ist und es an allgemeinen, auf alle Konfliktfälle anwendbaren Kollisionsregeln fehlt." (The resolution of conflicts between norms of different sources is difficult as public international law is lacking a hierarchy of norms comparable to domestic law and as there are no general rules of conflict that would apply to all cases of conflict.)

[63] *Ian Brownlie* – Principles of Public International Law, Fifth Edition 1998, at p. 3.

[64] As *Lauterpacht* explains : "The rights and duties of States are determined, in the first instance, by their agreement as expressed in treaties – just as in the case of individuals their rights are specifically determined by any contract which is binding upon them. When a controversy arises between two or more States with regard to a matter regulated by a treaty, it is natural that the parties should invoke, and the adjudicating agency should apply, in the first instance, the provisions of the treaty in question [...] Within these limits – which may be substantial [footnote omitted] – a treaty overrides international customary law and even general principles of law; […], *see Hersch Lauterpacht*, International Law – Collected Papers edited by E. Lauterpacht, Edition 1970, at p. 87.

[65] *Ibid.* (previous footnote) at p. 88.

> no conflict or inconsistency, or an expression in a covered WTO agreement that implies differently, we are of the view that the customary rules of international law apply to the WTO treaties and to the process of treaty formation under the WTO.[66]

229. Against this background, the following comments apply to the two issues raised in the Panel's question:

230. As regards the principle *clausula rebus sic stantibus* the European Communities, in its First Written Submission has already referred to the fact that the basis for the DSB authorization changes fundamentally once a Member has properly implemented.[67] This fact, however, does not lead to a *direct* application of the principle of *clausula rebus sic stantibus*. Indeed, there is no need for that, given that the obligation to cease the application of the suspension of concessions can be directly inferred from Article 22.8.

231. As regards the issue of a possible conflict between the principle of good faith and a DSB authorization, a few clarifications seem necessary. First, for the sake of accuracy it should be pointed out that the principle of good faith is a general principle of international law and not, as suggested in the question, a rule under customary international law.[68]

232. Second, we explained in the reply to Question 61 the relationship between the *principle* of good faith and a *presumption* of good faith (or more broadly, of compliance).

233. Third, assuming the question aims at the issue of a possible conflict between the presumption of good faith (or more generally of compliance) and that DSB authorization. In that regard the European Communities takes the view that no such conflict exists. The presumption that a Member is acting consistently with its WTO obligations is the very basis of the dispute settlement system. It is the reason why disputes are about inconsistency and not about consistency, why complaining parties assert violations and not the absence of a violation. That presumption is therefore also inherent to Article 22.8 and it is that provision which governs a Member's right to suspend obligations pursuant to a DSB authorization.[69]

Q64. If the Panel were not able to reach a conclusion on the first claim of the European Communities under DSU Article 23, do you think the Panel should proceed to examine the second claim of violation of Article 22.8 of the DSU?

234. The European Communities is not quite sure how to understand this question.

235. If this question refers to a situation where the Panel would find that there is no violation with regard to the two claims which the European Communities has set out under Article 23 (Article 23.1 in conjunction with Article 23.2(a) and 21.5, on the one hand, and Article 23.1 in conjunction with Article 22.8, on the other), then the European Communities would indeed request the Panel to proceed to examine the claim under Part II of the EC First Written Submission.

236. However, if the question means to refer to the possibility of a "non liquet" decision by the Panel on Article 23, the European Communities would contest that such a possibility exists. Panels

[66] Panel Report, *Korea – Procurement*, at para. 7.96.
[67] EC First Written Submission in DS320 (US), at para. 108.
[68] *See* only Appellate Body Report *US – Shrimp*, para. 158.
[69] Note that Article 22.8 is "primary" law compared to the DSB authorization, which, emanating from a body set up under the "primary" law (i.e. the agreements), is "secondary" law. It is worthwhile thinking about hierarchy issues in that regard. In the European Communities' view (admittedly drawing a direct analogy to EC law), the "secondary" law is subordinated to "primary" law requirements.

do not have the option of making "non liquet" decisions under the dispute settlement system. As the Appellate Body has emphasised in the context of the discussion on judicial economy and in reference to Article 3.7, second sentence, it is the role of the Panels to *secure a positive solution to a dispute*.[70] The Appellate Body has gone on to state that

> A panel has to address those claims on which a finding is necessary in order to enable the DSB to make sufficiently precise recommendations and rulings so as to allow for prompt compliance by a Member with those recommendations and rulings "in order to ensure effective resolution of disputes to the benefit of all Members." [footnote omitted][71]

237. It is, therefore, excluded, to simply "not reach a conclusion" on a claim that is not only central to, but indeed the very essence of the dispute at hand. If a panel were to do so it would be either diminishing the rights of one party or adding to the rights of the other. Article 3.2 DSU prohibits both such outcomes.

Q65. Canada and the United States have argued that the EC measure taken to comply with the recommendations and rulings of the DSB in the Hormones case are incompatible with Article 5.1 and 5.7 of the *SPS Agreement.* However, the European Communities does not make any reference to these provisions, either in its request for establishment of the panel, or in its first written submission. Do the parties believe that the Panel has, nonetheless, jurisdiction to review the compatibility of the EC implementing measure with Articles 3.3, 5.1 and 5.7 of the *SPS Agreement*? On what legal basis should the Panel consider itself entitled/not entitled to address the arguments of Canada and the United States in relation to the *SPS Agreement*?

238. The Panel's jurisdiction is governed by its terms of reference. As the Appellate Body has made clear

> The jurisdiction of a panel is established by that panel's terms of reference, which are governed by Article 7 of the DSU. A panel may consider only those claims that it has the authority to consider under its terms of reference. A panel cannot assume jurisdiction that it does not have.[72]

239. It seems clear, thus, that in the present case the Panel has no jurisdiction to address Articles 3.3, 5.1 and 5.7 of the *SPS Agreement*, which do not appear anywhere in the request for establishment of the Panel on which the Panel's terms of reference are based.

240. The issue is a perfect illustration of the problems arising if an implementing member is forced to bring a case alleging compliance, instead of the original complaining party bringing a case alleging non compliance (other aspects of which have been discussed elsewhere in this submission.[73]) The terms of reference become wholly devoid of their meaning and the panel's jurisdiction turns into a moving target depending on whatever allegations of inconsistency the "defending" parties will come up with. It is clear that the dispute settlement system is not designed to accommodate such a procedural constellation.

241. At best, one could venture to draw an analogy to affirmative defences. These are raised by a defending party without usually being referred to by the complaining party in its request for establishment of a Panel or its first written submission. The violation claims raised by the defending

[70] *See* only Appellate Body Report, *Australia – Salmon*, at para. 223.
[71] *Ibid.*
[72] Appellate Body Report, *India – Patents*, at para. 92.
[73] *See* for example, Question 62.

parties here, thus, would have to be assimilated to affirmative defences. The burden of proof to establish a *prima facie* case on such violations would, as with affirmative defences, then rest on the defending parties.[74]

Q66. In this particular case, would it be for the European Communities to prove the compatibility of its measure with Article 5.7 of the *SPS Agreement* because it applies certain aspects of that measure provisionally or would it be for Canada and the United States to demonstrate a violation of Article 5.7 because they consider that the EC measure is in breach of that provision? Could the parties discuss the application of the burden of proof in relation to Article 5.7 in light of the panels and Appellate Body findings with respect to that provision in *Japan – Agricultural Products II* and *Japan – Apples*?

242. The United States and Canada have the burden of asserting and making a *prima facie* case on, a violation of Article 5.7 of the *SPS Agreement*. There are at least two reasons for it. The first reason is the specific procedural constellation of this case: It is not for the European Communities to show compliance, but for the United States and Canada to show non-compliance, all the more if that non-compliance relates – as is the case with Article 5.7 – to an inconsistency which did not exist in the original case and is therefore not covered by the rulings and recommendations of the DSB.[75]

243. The second reason is, more generally, that according to the burden of proof rules, it is for the party asserting the affirmative of a particular claim or defence to make a *prima facie* case. Article 5.7, in the view of the European Communities does not constitute a defence (of the kind that Article XX of the GATT is) but is rather a special regime in relation to Article 5.1 of the *SPS Agreement.* Thus, it is not an exception any more than Article 3.3 of the *SPS Agreement* is an exception. It applies to provisional measures as opposed to the regular (definitive) measures under Article 5.1. As a regular claim, therefore, it is for the side alleging the violation, to make a *prima facie* case.

244. This reading is not contradicted by the case law so far. Indeed, it cannot be inferred from the case *Japan – Apples* that the burden of proof would be on the party that has adopted the provisional measure. Japan in that case, had voluntarily accepted the burden of proof. The Appellate Body was careful to stress that this assignment of the burden of proof to Japan by the panel was not challenged on appeal.[76]

245. The European Communities notes that on this point it shares the position of the United States. At the meeting of the DSB held on 10 December 2003 when the panel report in the case DS245 *Japan – Apples* was adopted, one of the points of disagreement expressed by the US delegate related to that panel's approach to the burden of proof under Article 5.7. According to the report of the meeting the delegate stated:

> The second point the United States wished to note was the Panel's conclusion that the Member maintaining the measure had the burden of establishing that it met the requirements of Article 5.7. Neither Japan nor the United States had supported this conclusion, taking the position that here, as with other claims, the complaining party had to bear the burden of proving that the measure did not meet the obligations set forth in a WTO provision.[77]

Q67. Do the parties consider that Article 5.7 applies only when no risk assessment can be made at all or also when scientific evidence exists but is insufficiently specific?

[74] *See* also reply to Question 62.
[75] *See* also reply to Question 65.
[76] Appellate Body Report, *Japan – Apples*, paras 175 and Footnote 316.
[77] WT/DSB/M/160 of 27 January 2004 at para 9.

246. It is generally accepted that Article 5.7 is applicable both when no risk assessment can be made at all, as well as when scientific evidence exists but is insufficiently specific or when the latest scientific evidence from any credible and objective source raises doubts or puts into questions the previously held scientific opinion about the safety or dangerous nature of the substances in question. This is very well explained by the Appellate Body *inter alia* in paragraphs 194 and 205 of its report in the hormones dispute.

Q68. Do all parties agree that the term "on the basis" in Article 5.7 of the *SPS Agreement* has the same meaning as "on the basis" in Article 5.1, i.e. that a "rational relationship" is required?

247. First, it should be noted that there is a difference in wording in the two Articles. Article 5.1 requires that SPS measures are "based on" a risk assessment, whereas Article 5.7 requires that provisional SPS measures be adopted "on the basis of" available pertinent information. Arguably, "on the basis of" would suggest a more remote relationship than "based on." That reading would tie in with the following substantive analysis:

248. It is clear that both "based on" and "on the basis of" suggest a – as the Appellate Body put it in the context of Article 5.1 ("based on") – "objective relationship between two elements."[78] The crux, however is, that that relationship is between *different elements* depending on whether one is in the context of Article 5.1 or in the context of Article 5.7. In the context of Article 5.1, it is the relationship between the SPS measure and a risk assessment, in the context of Article 5.7 it is the relationship between the (provisional) SPS measure and available pertinent information. That difference necessarily changes the nature of the relationship. Indeed, it would be illogical to apply the same standard of objective or rational relationship to a situation where there is full scientific evidence available and a situation where that evidence is insufficient.

Q69. During the *EC – Hormones* proceedings, the European Communities was of the view that "the scientific evidence concerning the need to regulate the use of hormones was in itself sufficient to justify its legislation and the European Communities did not need to rely on the exception provided for in Article 5.7 concerning cases where relevant scientific evidence was insufficient" (DS26/R/USA, para.4.239). Does this mean that "the evidence concerning the need to regulate the use of hormones generally" is different from the specific evidence concerning the health risk associated with the administration of hormones in animals for growth promotion purpose? Is there sufficient evidence concerning the latter?

249. It is not entirely clear why only this sentence is cited from paragraph 4.239, which is much longer. It would also seem that the reply to this question is intimately linked to the replies to Question No 19 above (why is the ban on five hormones now provisional), Question 30 (insufficiency of the information), Question 34 (safety of the hormones), Question 70 (available pertinent information), Question 73 (evolution of scientific understanding) and all other Questions dealing with the different steps of the risk assessment. The European Communities respectfully refers the Panel back to its replies to these questions.

250. The European Communities found that the evidence which is normally taken into account for the assessment of substances of this kind, whether of general or specific nature, is insufficient, inconclusive and contradictory for five of these hormones. Indeed, the new scientific studies that have been initiated since the DSB recommendation in the hormone case, in order to address the scientific information that was found by the panel and the Appellate Body to be missing, have now identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge

[78] Appellate Body Report, *EC – Hormones*, at para. 189.

now available on these hormones, which have together reinforced the need for even more studies. Evidence from other sources is also putting in doubt the sufficiency of the basis upon which the defending members and other bodies have come to the conclusions that the residues of these hormones in meat from animals treated for growth promotion (see, e.g., the study contained in the exhibit to Question No 34 above).

251. The previous Directive 96/22/EC was drafted in 1995 and adopted in 1996 as a codification of the pre-existing European Community measures in this area. This happened at a time where international guidance on how to perform a risk assessment was not yet available to tackle situations where scientific information was insufficient to conclusively assess a particular risk, in accordance with a member's chosen level of health protection. For example, at that time there did not exist standards nor guidelines from the Codex Alimentarius Commission on how to perform a risk assessment and risk analysis. Moreover, the provisions of Article 5.7 have now been clarified in a number of panel and Appellate Body reports, starting with their reports in the *hormones* case, which was not the legal situation before 1996.

252. Substantive international discussions have lead to the development of the Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius Commission[79] after 1996. This has only been adopted by the Codex Alimentarius Commission in at the 26th Codex Alimentarius Commission meeting at Rome in July 2003. The relevant concepts developed there have been taken into account by the European Communities and have now influenced the drafting of its framework Food Law, namely Regulation 2002/178/EC.

253. It follows that at that time the European Communities believed the information was sufficient – in light of the general knowledge available at the time - because it had identified potential risks which were found to be unacceptable in respect of its own chosen level of protection, and because it could not complete a risk assessment in the sense explained by the Appellate Body and the Panel for the first time in the hormones case, nor according to the Codex Alimentarius guidelines on risk analysis which were adopted much later. This is for all five hormones, and obviously for the melengestrol acetate (MGA).

254. As regards the possible differences between the evidence concerning the health risk associated with the use of hormones generally or with the administration of hormones in animals for growth promotion purposes, they are further elaborated in the reply to the next Question. The short reply is that evidence from both of situations is relevant for the performance of a risk assessment in the sense of the *SPS Agreement*, because both sources of evidence impact upon and inform each other. It is also clearly in the case of these hormones the outcome of the European Communities' risk assessment that the specific evidence concerning the health risk associated with the administration of hormones in animals for growth promotion purpose is insufficient and inconclusive, except for oestradiol 17b.

Q70. Having regard to the statement of the United States in paragraphs. 151-152 of the first US written submission, the Panel notes that Article 5.7 of the *SPS Agreement* talks about "available pertinent information" on the health risk. In the parties' views, does this mean that the "available pertinent information" under the circumstances of the current disputes refer to the information on risks associated with the consumption of meat from animals treated with hormones for growth promotion purposes according to good veterinary practice? Or, does it refer to the risk of the five hormones to human health generally?

[79] see at ftp://ftp.fao.org/codex/Publications/ProcManuals/Manual_14e.pdf.

255. Both the information concerning the health risk associated with the use of hormone generally and the information on risks associated with the administration of hormones in animals for growth promotion purposes according to GVP, and the consumption of meat thereof, are two distinct but complementary and necessary components of an overall risk assessment of the consumption of meat from animals treated with hormones for growth promotion purposes.

256. This has to be understood as two concentric circles of evidence, both informing the risk assessment, the big circle, with respect to the general use of hormone, and the interior circle, related to the specific use considered. It is only if the latest stage of risk characterization of the inner circle can be reached, once hazards would have been identified and characterised, and exposures properly measured, that the specific risks of the inner circle, for the specific use at stake, could be singled out from the risks of the big circle.

257. In the context of Article 5.7 of the *SPS Agreement*, and under the circumstances of the current disputes, "available pertinent information" therefore refers to either types of information, if one or the other warrants that a provisional measure be taken.

258. As an illustration, if a serious hazard is identified for the general use of a product, before that hazard can be properly characterized in the context of a specific use, and the relevant hazard exposure assessment properly measured for that specific use, the serious hazard identified should certainly be "available pertinent information" in the context of the specific use in order to enable the adoption of provisional measures to circumscribe that potential risk. Ruling to the contrary would seriously undermine public health, for the least, or even be criminal.

Q71. Article 5.7 of the *SPS Agreement* requires that a Member review the measure within a reasonable period of time. In the parties' view, how long should this reasonable period of time be in this case? At which point of time should the calculation of the reasonable period of time start? Has the European Communities conducted such a review after the adoption of Directive 2003/74/EC in September 2003? What is the plan of the European Communities to conduct such review?

259. The length of a reasonable period of time varies from case to case, and depends notably on how quickly and how much additional pertinent information is obtainable. It is noteworthy for instance, that within the European Communities, differences in the constitutional requirements, as compared to the legal system of other members, may require different timings for amending a measure of this kind. It took indeed virtually three years between the time of the proposal of Directive 2003/74/EC and its final adoption and publication.

260. Certainly, the start of the reasonable period of time to review a measure can not seriously start before the provisional measure being enacted, i.e. implemented, namely 14 October 2004 in the case of Directive 2003/74/EC.

261. The whole chronology of the current case, after the Appellate Body report in the *EC – Hormones* case, has indicated a permanent review of the available information and of the risk assessment. The first opinion of the SCVPH was issued in April 1999 and, as explained in recital 8 of Directive 2003/74/EC, the SCVPH reviewed its assessment in May 2000 in the light of new information, including the JECFA opinion of February 2000, as well as in April 2002 in the light of the most recent scientific data.

262. In the present situation, recitals 10, 12 and article 9 of Directive 2003/74/EC set out already identified deadlines to review some elements of the scientific evidence, which related to the

therapeutic and zootechnical uses, and requires that additional information be sought, and that the measure be kept under regular review with a timely presentation of any necessary proposals.

263. The recent draft report from the UK authorities (Exhibit US – 20) has already been referred by the European commission to the European Food Safety Authority for evaluation (EFSA being the new scientific independent advisory body responsible for performing the assessment of risks for this kind of substances).

264. Furthermore, a review of the 2002 SCVPH opinion has been commissioned by EFSA, which has issued on 12 September 2005 a new call for new scientific data and research, from 2002 onwards, on substances with hormonal activity which may be used for growth promotion purposes in bovine meat.[80]

Q72. Please explain what you understand to be the relationship between Article 3.1 and Article 5.7 of the *SPS Agreement*?

265. The European Communities understands this question to be inquiring whether, in the presence of an international standard, guideline or recommendation that is based on a risk assessment it is possible to adopt a provisional sanitary measure on the grounds that the relevant scientific evidence is insufficient.

266. In the European Communities' view, this is indeed possible. A Member may disagree with the risk assessment for scientific reasons and, in particular, on the issue of whether the scientific evidence relied upon is sufficient. Such disagreement may stem from differences of views on scientific questions such as methodology, data interpretation etc.; it may also result from the fact that in order to meet a higher level of protection, the Member concerned may require more information than what is provided in the risk assessment in question. Article 3.3 of the SPS Agreement applies, at least by analogy.

267. As a concrete example, the JECFA study referred to by the defending parties did not take into account the data obtained in the seventeen studies which had been performed upon the initiative and with the funding of the European Communities.

Q73. Do you consider it possible that scientific evidence may be judged to be sufficient to undertake a risk assessment at a particular point in time, and yet considered to be insufficient for the same purpose several years later? Does the fact that a significant number of scientific studies have been undertaken with regard to these potential risks in the intervening years have any relevance for your response? Does the existence of international standards have any relevance? Please explain?

268. The first part of the question is obvious. The 20th century's history of Public health is full of such cases in members, whereby a risk assessment at a given point in time was felt to be based on sufficient evidence, while at a later stage new scientific evidence had contradicted previous evidence, and the same situation required the conduct of further scientific studies and the review of its risk assessment.

269. This tautology is the simple consequence of the dynamic nature of scientific knowledge and from the scientific dialectic in research. New findings in scientific research improve scientific understanding, which in terms identifies new questions to resolve, which leads to further research.

[80] *See* http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/c_238/c_23820050928en00050006.pdf.

270. It is also noteworthy that this goes either way, that is a product may be initially banned or be strictly controlled on the basis of its initial risk assessment, while further scientific information may later suggest that risks may have been originally overestimated and in turn require further scientific information to assess more accurately these risks. Vice versa, a product may have been authorised on the basis that its risk assessment indicated a satisfactory level of protection, while later scientific studies may identify new potential impacts or hazards that require further studies and research to be accurately characterised.

271. This evolution in the scientific understanding of a particular risk assessment may not only come because new scientific evidence may identify new risks (or new reasons of safety), but also because new risk assessments may be performed according to evolving international standards. For instance, there were no international standards or guidelines on how to perform a proper risk assessment at the time of our initial measure, while now there are, which identifies the recommended steps (e.g. risk characterization, dose/exposure response, etc.). These were developed after the first hormone panel and the Appellate Boy reports.

272. There is a plenty of such examples where this occurred, but just to cite a few various ones in public health, here are some: BSE, asbestos, AIDS, DDT, softenon, even radioactivity or some food colouring or flavouring substances.

273. In the case at stake in these proceedings, most importantly, not all scientific evidence was available at the time, and the new scientific studies have certainly modified the content of the risk assessment. By identifying new hazards, it also requires a new risk assessment to be performed to fill the gaps and the uncertainty identified in the scientific evidence.

Q74. Assuming the Panel deems it necessary to determine whether the European Communities revised measure complies with certain provisions of the *SPS Agreement*, do the parties consider that the consultation of scientific experts would be necessary or only useful? What would be the issues on which experts should be consulted? To the extent feasible, should the Panel consult the experts consulted in the *EC – Hormones* case?

274. The scientific issues that are relevant for the use of hormone having oestrogenic, androgenic, or gestagenic action, used as growth promoters in meat production, are extremely complex and difficult. The European Communities' scientific Committees have been working on them for several years. The European Communities does not believe that it is necessary for this Panel to look into any scientific issues to make its necessary findings and rulings within its terms of reference in this particular case.

275. However, the European Communities does not believe that the Panel would have the expertise to decide on such issues itself, should the Panel decide to go down of deciding the scientific issues at stake. In such a scenario, the European Communities believes that the consultation of scientific and technical advice would be absolutely necessary. In such an unlikely scenario, experts should be consulted. However, the European Communities considers that this Panel cannot consult the experts that were used in the original *EC – Hormones* case because three of the five experts are now clearly known to have worked and have close ties with the pharmaceutical industry, the views of one expert were considered not relevant by the Appellate Body in this case, and the fifth one has subsequently conducted scientific studies for the European Commission. Therefore new experts will have to be chosen.

ANNEX B-2

REPLIES OF CANADA TO QUESTIONS POSED BY THE PANEL AFTER THE FIRST SUBSTANTIVE MEETING

(3 October 2005)

Questions to Canada:

Q35. Canada claims that it is entitled to maintain its suspension of concessions or other obligations as long as the DSB has not decided to withdraw its authorization. However, one may argue that, even with the authorization of the DSB, the Member concerned is not obligated to impose the retaliatory measures. In addition, Article 22.8 provides that the suspension of concessions "shall only be applied until such time as the measure found to be inconsistent ... has been removed". In that context, why does Canada believe that a decision of the DSB is necessary for it to remove its retaliatory measures?

1. Canada does not believe that a decision of the DSB is necessary for it to remove its retaliatory measures. As the Panel notes, a Member is not obligated to impose retaliatory measures even when it has authorization to do so. Nor does it have to wait for a decision of the DSB before it may remove them. The issue, however, is not when a Member may remove its retaliatory measures but when it must do so. According to Article 22.8 of the DSU, it must do so when, *inter alia*, the measure found to be inconsistent has been "removed" (*i.e.*, brought into compliance). In the absence of agreement between the disputing parties that the inconsistent measure has been "removed", the question that arises is who may make that determination.

2. In accordance with Articles 21.6 and 22.8, second sentence, of the DSU, disputes remain under the surveillance of the DSB until they are resolved. As a result of this ongoing surveillance, and in the light of an explicit authorization by the DSB under Article 22.7 to suspend concessions, it is for the DSB to confirm that the inconsistent measure has been removed.

3. In the circumstances of this case, the EC claims that it has removed its measure and Canada disagrees. It therefore is the responsibility of the DSB to determine whether the EC has done so before Article 22.8 of the DSU can have been satisfied. A decision by the DSB to terminate the authorization is simply a consequence of the confirmation by the DSB that the conditions of Article 22.8 have been met.

Q36. With reference to paragraph 47 of Canada's first written submission, could Canada explain how the suggested initiation of "new proceedings in which [the EC would request] the Panel to determine the actual compliance of a measure [the EC] has adopted to implement the recommendations and rulings of the DSB" would operate under the WTO dispute settlement system?

4. Paragraph 47 of Canada's First Written Submission refers to panel proceedings *de novo*. The EC would initiate panel proceedings, as it has done in the present case, alleging that one of the conditions of DSU Article 22.8 has been fulfilled. The EC would assume the burden of demonstrating to the panel that its measure is now compliant with the recommendations and rulings of the DSB in *EC – Hormones*, that the EC has "removed" the measure that was previously found to be non-compliant, and that consequently, pursuant to DSU Article 22.8, Canada is no longer entitled to suspend concessions. If the EC had assumed that burden at the outset of these proceedings, as it

appears to have done in Part II of its First Written Submission, then the current proceedings would replicate the scenario set out above.

5. As a responding party, Canada would be entitled to demonstrate, by way of defence, other inconsistencies of the EC's measure with the covered agreements. Such inconsistencies would be an affirmative defence on Canada's part in respect of the alleged violation of DSU Article 22.8. By demonstrating that the EC's measure is inconsistent with other provisions in the covered agreements, Canada would effectively disprove the EC's claim that the measure previously found non-compliant had been "removed" (within the meaning of DSU Article 22.8). The burden would be on Canada to demonstrate the existence of any other inconsistencies on the part of the EC. A responding party is entitled to put forward an exception or other affirmative defence regardless of the terms of reference of the panel.[1]

6. If such a panel were to find that the EC's measure complies with the recommendations and rulings in *EC – Hormones* and Canada were not able to demonstrate any inconsistency with other obligations, the panel would then make a recommendation to Canada that it lift the suspension of concessions. The adoption of such a report would constitute implicit revocation of the DSB's authorization to Canada to suspend concessions.

7. If the panel were to find that the EC measure does not comply with the recommendations and rulings, or is inconsistent with other obligations of the EC in a covered agreement, it would not make a recommendation to Canada.

Q37. Other than through recourse to an Article 21.5 panel, is there any other manner whereby the EC can seek to obtain a *multilateral* determination on whether or not its compliance measure has removed the WTO inconsistency?

8. Adoption by the DSB of a panel report resulting from the process described in Canada's answer to question 36 above, with a finding that the EC had complied, would constitute multilateral confirmation of the EC's compliance.

9. The parties could also, by agreement, have recourse to arbitration pursuant to DSU Article 25, the result of which would be notified to the DSB.

Questions to Canada and the United States:

Q43. Do Canada and the United States agree with the European Communities' statement in paragraph 32 of its first written submission that the specific forms described in paragraph 2 [of Article 23 of the DSU] do not exhaust the list of prohibited unilateral actions and its reference to the Panel Report in *US – Section 301 Trade Act*? Why?

10. Yes, Canada agrees. Article 23.2 of the DSU is not exhaustive but sets out certain "specific and clearly-defined forms of prohibited unilateral action" covered by the general rule in Article 23.1.[2] However, any action impugned under Article 23.2 must first fit under the circumstances described in Article 23.1. In other words, in order for there to be a violation of either the general obligation to

[1] See *United States – Measure Affecting Imports of Woven Wool Shirts and Blouses from India*, Report of the Appellate Body, WT/DS33/AB/R and Corr.1, adopted May 23, 1997, at p. 14; *United States – Tax Treatment for "Foreign Sales Corporations" – Recourse to Article 21.5 of the DSU by the European Communities*, Report of the Appellate Body, WT/DS108/AB/RW, adopted January 29, 2002, at para. 133 [*US – FSC (Article 21.5 – EC)*]; and *India – Quantitative Restrictions on Imports of Agricultural, Textile and Industrial Products*, Report of the Appellate Body, WT/DS90/AB/R, adopted September 22, 1999, at para. 136.

[2] See Canada's First Written Submission, at para. 71.

"have recourse to, and abide by, the rules and procedures" of the DSU set out in Article 23.1, or one of the specific prohibitions enumerated in Article 23.2, it has to be established that a Member is "seek[ing] the redress of a violation of obligations" under the covered agreements.

11. The concessions to the EC that Canada is currently suspending are not to redress an alleged WTO inconsistency of the EC's new measure. The concessions are being suspended on the basis of a DSB authorization which has not been terminated nor have the conditions required for its removal been established by the EC. Canada's action in respect of the original measure – which is at issue here – is thus fully consistent with Article 23.1's admonition that Members shall abide by the rules and procedures of the DSU.

Q44. Do Canada and the United States agree with the European Communities that whenever there is a violation of Article 23.2 of the DSU, there is always a violation of Article 23.1?

12. If a Member is seeking redress of a perceived WTO violation by means of one of the specific forms of prohibited unilateral action set out in paragraphs (a) to (c) of Article 23.2 of the DSU, there would also be a violation of the general rule to have recourse to and abide by the rules and procedures of the DSU set out in Article 23.1 of the DSU. Article 23.2 is an illustration of the general rule in Article 23.1 of the DSU and applies only when a Member is seeking redress of a WTO violation. This is apparent from the *chapeau* of Article 23.2, which includes the phrase "in such cases", thereby referring to when Members "seek the redress" of a WTO violation.

Q45. Do Canada and the United States consider that the European Communities could have, as the party having to comply, effectively made a recourse to Article 21.5, in the light of the recourse to Article 21.5 by the European Communities in the *EC - Bananas III* case? If yes, and in light of Article 6 of the DSU, who would be the complainant, and what would be the complaint?

13. Under DSU Article 21.5, the EC could initiate the proceeding and request a ruling that the EC has complied with the recommendations and rulings of the DSB in *EC – Hormones*. The EC would be the "complaining party" in a broad sense, *i.e.*, the party that would initiate the proceedings. Canada notes that DSU Article 6.1 refers to a "complaining party" but DSU Article 6.2 refers to "the applicant". The "complaint" in a broad sense, *i.e.*, the subject matter of the proceeding, would be that the EC has complied with the recommendations and rulings of the DSB. The EC would have the burden of making a *prima facie* case to that effect and would have to put forward sufficient evidence and arguments to meet that burden.

14. A proceeding under DSU Article 21.5 would not necessarily require the involvement of a respondent party. The absence of a respondent party would not deprive a panel of jurisdiction. Even without the participation of a respondent party, legal consequences will flow from the recommendations and rulings of the DSB when it adopts panel and Appellate Body reports.

15. The report in *EC – Bananas III (Article 21.5 – EC)* demonstrates that the DSB established a DSU Article 21.5 panel for the purpose of having the EC seek confirmation of the WTO consistency of its own measure, and that the procedure under DSU Article 21.5 was used by the EC to that effect.[3]

Q46. Presuming that Canada and the United States are interested in a prompt resolution of this dispute, why have they not initiated the expedite procedure of Article 21.5 to challenge the EC implementing legislation as they do in these proceedings?

[3] *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Article 21.5 by the European Communities*, Report of the Panel, WT/DS27/RW/EEC, April 12, 1999, unadopted.

16. As Canada has explained in its answer to question 50, Members of the WTO have a variety of means and avenues through which to deal with existing trade disputes. Although Canada has no obligation to initiate WTO dispute settlement proceedings, the initiation of proceedings under DSU Article 21.5 is an option that Canada may exercise depending on the particular circumstances of a case. In this case, Canada chose not to exercise that option.

Q47. With reference to the European Communities' statement in paragraph 62 of its oral presentation, could Canada and the United States confirm whether, and explain why, the implementation of the *EC – Hormones* case has "practically not been on the DSB agenda since July 1999?

17. According to Article 21.6 of the DSU, the implementation of adopted recommendations and rulings remains under the surveillance of the DSB until the dispute is resolved. Article 22.8, second sentence, of the DSU provides that DSB surveillance continues even after concessions have been suspended. Article 21.6 of the DSU also provides that disputes will be placed on the meeting agenda of DSB meetings, but provides the DSB with the discretion not to place it on the agenda. In other words, while the DSB has the discretion not to place a dispute on its formal meeting agenda, it does not have the discretion to remove a dispute from its surveillance until it is resolved.

18. The *EC – Hormones* dispute remained on the DSB agenda until the adoption of the authorization to suspend concessions, prior to which time the EC provided regular reports on its plans to implement the recommendations and rulings of the DSB. Once it became clear, however, that the EC would take some time to implement and that the implementation reports were substantially the same from meeting to meeting, the DSB exercised its discretion under Article 21.6 and removed the item from its meeting agenda until there was something new to report. The fact that the EC's implementation of the recommendations and rulings in *EC – Hormones* was removed from the DSB's meeting agenda does not mean, however, that it was no longer legally under the surveillance of the DSB.

19. The EC, in fact, acknowledged that its implementation remained under the surveillance of the DSB when it notified in a communication to the DSB that it had adopted a measure to implement the recommendations and rulings in *EC – Hormones*.[4] For the EC now to call into question the ongoing surveillance of the DSB by arguing that the dispute has "practically not been on the DSB agenda since July 1999" is simply an effort to elevate form over substance.

Q48. The European Communities states in paragraph 44 of its oral statement that "a 'determination' ... need not be pinned down to a specific statement in a specific form, it is the whole conduct a WTO Member is displaying that needs to be looked at". Why would this not be the case here? If the sum of US and Canadian statements, actions and arguments are not a unilateral determination of violation, isn't it at least evidence of their disagreement with the European Communities within the meaning of Article 21.5?

20. A determination within the meaning of Article 23.2(a) of the DSU can only occur, as specified in the *chapeau* of Article 23.2, "in such cases" where a Member seeks the redress of an alleged WTO violation. Canada acknowledges that there is a disagreement regarding the WTO consistency of the EC's new measure within the meaning of Article 21.5 of the DSU. However, this "disagreement" is not tantamount to a "determination" within the meaning of Article 23 since Canada has not acted to seek redress against the EC for this alleged violation. Unlike what is argued by the

[4] *EC – Hormones*, Communication from the European Communities, WT/DS26/22, WT/DS48/20, October 28, 2003.

EC, it cannot be inferred from Canada's continued suspension of concessions that it is seeking the redress of a violation other than that identified in *EC – Hormones*; nor, therefore, can it be inferred that Canada has made a "determination" with regard to the EC's new measure in contravention of Article 23.2(a) of the DSU.

21. The legal basis for Canada's suspension of concessions is not Canada's views on the inconsistency of the EC's purported implementing measure but rather the absence of affirmative multilateral confirmation of the EC's compliance and the ongoing validity of the DSB authorization. Until such time as the DSB authorization is terminated, Canada's assessment of the WTO consistency of the EC's new measure remains unrelated, and irrelevant, to Canada's continued suspension of concessions.

Q49. Can the United States and Canada explain whether they provided answers to the European Communities' requests for information on scientific studies made by the European Communities? If not, why?

22. The EC sent a letter dated April 8, 1998, to the Government of Canada requesting the full scientific studies including raw data on which Canada based its decision to authorize the use of the six hormones in question for growth promotion in cattle.

23. Health Canada responded in a letter dated August 4, 1998, that the Government of Canada is required by Canadian law to hold the requested data and studies in confidence and cannot by law release this information to a third party. In this same letter, Health Canada provided the full names and addresses of each of the firms with proprietary rights to the information the EC had requested, as these are the only parties permitted under Canadian law to release the requested information, and invited the EC to contact these firms directly to request the data and studies.

24. The EC subsequently repeated its request to Canada in another letter, and Health Canada responded on February 26, 1999, further clarifying that Canada's *Access to Information Act* prevents Canada from disclosing any record that contains confidential scientific or technical information supplied to the government by a third party. Canada also noted in this letter that the EC had not yet contacted the companies concerned, *i.e.*, those with proprietary rights to the information the EC had requested. Canada is not aware that the EC has since contacted these firms. Canada received no further requests from the EC for this or other related information.

Questions to all parties:

Q50. Could each party provide the Panel with a detailed account of the efforts it has made to solve this dispute since the notification by the European Communities of its implementing measure in 2003?

25. Members of the WTO have a variety of means and avenues through which to discuss existing or potential trade disputes. Some of these are more formal than others; informal discussions prior to the commencement of WTO consultations under DSU Article 4 were "diplomatic" in nature and therefore normally considered to be confidential. Canada can confirm that through its Missions in Brussels and Geneva, as well as through capital-based officials, it held a series of informal discussions with various officials of the EC Commission soon after the announcement by the EC of its purported compliance measure. These discussions were aimed at resolving both the substantive and the procedural elements of the current dispute.

26. More formally, since the implementation of the EC's 2003 Directive, Canada has repeatedly indicated – including through comments made at meetings of the DSB – its desire to discuss with the EC the reasons why it considers it has brought itself into compliance.

27. Canada and the EC held a videoconference in April 2004, with the express purpose of clarifying the alleged scientific basis for the EC's claims to have brought itself into compliance. The EC was unable to provide complete responses to many of Canada's questions presented in this exchange. Canada has continued to express its willingness to engage in further technical discussions, but none has taken place.

Q51. Having regard to the first claim of the European Communities, in a post-retaliation phase, if a suspension of concessions is consistent with Article 22.8, can it nevertheless be inconsistent with Article 23 of the DSU? Under what circumstances? Please elaborate.

28. No. A measure suspending concessions that is consistent with Article 22.8 of the DSU cannot at the same time be inconsistent with Article 23. A measure that is authorized by the DSB cannot be conduct that constitutes a unilateral determination for the purposes of DSU Article 23.2(a). A determination for purposes of a breach of Article 23.2(a) involves conduct by a WTO Member that is otherwise prohibited. If the suspension of concessions is still authorized for the purposes of Article 22.8, it cannot at the same time be prohibited for the purposes of Article 23.2(a).

29. The EC has attempted to define Articles 23.2(a) and 22.8 in a manner that makes them operate independently of one another. There are, of course, circumstances in which a breach of Article 23 can be found that does not involve Article 22.8 (such as when there is no DSB authorization). However, when the conduct complained of is the same for the purposes of both provisions – in this case, the suspension of concessions – these provisions cannot be interpreted and applied in isolation of each other.

Q52. In the *US – FSC* case, the European Communities suspended the application of its suspension of concessions and then initiated an Article 21.5 procedure because it considered that the US implementing legislation was inconsistent, *inter alia*, with the SCM Agreement. Please give your views on whether it would also be possible to request the establishment of an Article 21.5 panel while continuing to apply the suspension of concessions pending the outcome of the Article 21.5 procedure?

30. Yes, it would be possible for a WTO Member to request the establishment of an Article 21.5 panel while continuing to apply the suspension of concessions authorized by the DSB, pending the outcome of the procedure under DSU Article 21.5.

31. Notwithstanding the decision of the EC in *United States – FSC*, a WTO Member that has acted on a DSB authorization to suspend concessions is not obliged to reinstate concessions as a precondition to a challenge of compliance of another Member's implementation measure, to discontinue the suspension of concessions. In the absence of a "mutually satisfactory solution", Members are entitled to look to the DSB for multilateral confirmation that their suspension of concessions is no longer authorized. There is no obligation to discontinue an authorized suspension unless there is multilateral confirmation that the measure taken to comply with the recommendations and rulings is consistent with the covered agreements. Seeking such confirmation would be the purpose of a proceeding under DSU Article 21.5.

Q53. Are the parties of the view that, in the absence of a challenge by the implementing party against the continued suspension of concessions, such suspension can continue for an indefinite period of time, even though they are supposed to be only temporary. If not, what provision of

the DSU can serve as a legal basis for *preventing* the suspension of concessions for an indefinite period of time?

32. While Article 22.8 of the DSU specifies that suspension of concessions is to be only "temporary", it does not impose actual time limits on the duration of that suspension of concessions. The effective time limit, however, is always within the control of the implementing Member, in this case the EC. When there is multilateral confirmation that the measure found to be inconsistent has been removed, such that the conditions of Article 22.8 have been satisfied, the time limit expires and the suspension of concessions is no longer justified. The failure of the implementing Member to seek such multilateral confirmation, however, cannot be used to suggest that the Member suspending concessions is attempting to do so "indefinitely".

Q54. Could the parties provide the Panel with their understanding of the meaning of the term "measure" in Article 19.1 of the DSU and of the term "measures taken to comply with the recommendations and rulings [of the DSB]" in Article 21.5 of the DSU? More particularly, do the parties consider that a measure taking, e.g., the form of a ban remains the same measure, irrespective of the change in supporting legislation, as long as it is a ban? If not, what makes a "measure taken to comply" different from the measure which had to be brought into conformity?

33. As DSU Article 19.1 applies generally to the dispute settlement system, the term "measure" in DSU Article 19.1 has a broader meaning than "measures taken to comply with the recommendations and rulings [of the DSB]" in DSU Article 21.5.

34. The EC is not contesting that Directive 96/22/EC, as amended by Directive 2003/74/EC, qualifies as a "measure taken to comply" within the meaning of DSU Article 21.5. Canada and the EC disagree about the compliance of the EC's measure with the recommendations and rulings of the DSB in *EC – Hormones*; not about whether the EC's measure is a "measure taken to comply" within the meaning of DSU Article 21.5.

Q55. When does the legal effect of the DSB authorization lapse and by what procedures? Where parties disagree on the consistency of a notified implementing measure effected after the DSU retaliation authorization, does the DSU authorization lapse at the time when (i) the DSB makes a decision of compliance with respect to the implementing measure, or (ii) the implementing measure is in actual compliance regardless of whether the DSB has made a determination of compliance or not, or (iii) the Member concerned notifies its implementing measure to the DSB and declares its compliance, or (iv) the DSB makes a specific determination to terminate its previous retaliation authorization?

35. Option (i) is the correct interpretation of when the authorization lapses. That is, where parties disagree whether a measure originally found non-compliant has been brought into compliance, the DSB authorization ceases to have effect when compliance has been confirmed multilaterally by the DSB. The DSB need not formally revoke the authorization; rather, the end of the authorization may be implicit in the adoption by the DSB of panel and/or Appellate Body findings that an implementing measure is compliant. Of course, there may be circumstances in which the DSB would also formally terminate the authorization at the same time that it confirms compliance, in which case option (iv) would also apply.

Q56. Article 21.5 of the DSU provides that where there is a "*disagreement* as to the existence or consistency with a covered agreement of measures taken to comply with ... such dispute shall be decided through recourse to these dispute settlement procedures." Since Article 21.5

provides that "such dispute *shall* be decided"[5] through recourse to [the DSU]", would the parties consider that either of them has an obligation to refer the matter to the DSB under Article 21.5? If yes, why?

36. No, there is no obligation on either party to initiate proceedings under DSU Article 21.5. The obligation is for WTO Members, once they decide to resolve their disagreements, to do so within the framework of the DSU and not outside.

Q57. How would you distinguish between expressing "disagreement" over the WTO compatibility of a measure taken to comply with recommendations and rulings adopted by the DSB for the purpose of deciding whether or not to start an Article 21.5 procedure and a unilateral "determination" of WTO compatibility of such a measure?

37. A WTO Member may examine and analyze the measures of another Member and arrive at certain views on the compliance of those measures. Such examination and analysis may result in the Members disagreeing about the WTO consistency of the measures. This would not constitute a "determination" within the meaning of DSU Article 23.2(a). In the light of Article 23.1, a "disagreement" only becomes a "determination" once a Member takes action to "seek the redress of a violation of obligations or other nullification or impairment of benefits under the covered agreements or an impediment to the attainment of any objective of the covered agreement". An example of a "determination" within the meaning of Article 23.2(a) would be the hypothetical case of Canada suspending further concessions to the EC, and thereby exceeding the level of suspension of concessions authorized by the DSB, in response to the alleged WTO inconsistency of the EC's implementing measure.

38. A disagreement in and of itself is not sufficient to constitute a violation of Article 23. Rather, there must be action outside the rules and procedures of the DSU that seeks redress of the perceived violation before there can be a violation of Article 23.

Q58. In a situation where an Article 21.5 panel, requested to examine the compatibility of an implementing measure, finds that only partial compliance has been achieved, what is the procedure available to the original complainant:

(a) Can it continue to apply the suspension of concessions initially authorized by the DSB?
(b) Does it need to request a new authorization?
(c) Can the implementing party object to the level of suspension and request an Article 22.6 arbitration to determine a new level of suspension of concessions?

39. When a panel finds that only partial compliance has been achieved, it is effectively finding that the authorized level of suspension of concessions is no longer equivalent to the level of nullification and impairment caused by the "partially compliant" implementing measure, as is required by Article 22.4 of the DSU. There is no express mechanism in the DSU by which the level of suspension of concessions can be readjusted to be equivalent again to the level of nullification and impairment. However, any difficulties caused by the absence of such a mechanism arise in any proceedings that review a measure taken to comply, regardless of who initiates the proceedings.

40. The fact that there are systemic difficulties in readjusting the levels does not mean that this scenario creates insurmountable hurdles in resolving a dispute. If such a situation were to occur, the parties to the dispute would work out in good faith between themselves how the level would be

[5] Emphasis added by the Panel.

readjusted. The initial authorization would remain in effect, but the level of suspension of concessions could be modified by the parties, either through mutual agreement or by recourse to Article 25 arbitration.

41. Therefore, only option (a) is appropriate, where the party suspending concessions would continue to do so, albeit at an appropriately adjusted level. Neither option (b) nor option (c) is appropriate because Article 22.7 specifically prohibits a new arbitration to establish the level of nullification and impairment, which would be required to obtain a new authorization.

Q59. Is Article 23 of the DSU applicable to a suspension of concessions under a previous authorization of the DSB and in the absence of a new DSB decision of termination of the previous authorization?

42. Article 23 of the DSU does not apply to authorized suspension of concessions in the absence of some intervention by the DSB that – either explicitly or implicitly – terminates the DSB authorization. WTO Members that continue to suspend concessions under such authority – even in the face of an implementing measure by the other Member – are not "seeking redress" of a perceived violation. For a Member to be found in breach of Article 23 of the DSU, it must have acted in response to a perceived violation by another Member of that Member's WTO obligations. If the DSB authorization to suspend concessions remains in effect, a WTO Member that simply continues to suspend concessions on the basis of this authorization cannot be found to have engaged in conduct prohibited by Article 23. In such circumstances, the Member's conduct continues to be based on the DSB authorization and is therefore unrelated to the perceived compliance or non-compliance of the implementing measure.

Q60. Having regard to the US reference to the DSU negotiations in footnote 202 of its first written submission, could the parties indicate which proposals have been made in that context that would represent *amendments* to the current text of Articles 21.5, 22.8, 23.1 and 23.2(a) of the DSU?

43. With respect to the relationship of the present case to the DSU review process, the DSU review process is entirely separate from and unrelated to the issues the Panel has been called upon to resolve. The information requested concerns proposals by various WTO Members for future amendments to the text of the DSU. Canada respectfully submits that it is the Panel's responsibility to resolve the issues presented to it in the present case on the basis of the current text of the DSU (and any other relevant covered agreements). The amendments that have been proposed to the text of the DSU are therefore irrelevant to the issues the Panel has been asked to address under its terms of reference. This being said, the documents that contain proposals for amendments to Articles 21.5, 22.8, 23.1 and 23.2(a) of the DSU are contained in working documents JOB(04)/52, JOB(05)/47 and JOB(05)/71. An earlier proposal was contained in WTO document TN/DS/W/32.

Q61. How does the principle of good faith affect the allocation of burden of proof in these two disputes? What kind of presumption should be made by the Panel if/when applying this principle? Does the application of this principle under the circumstances of the present disputes lead to the conclusion that the EC's implementing measure shall not be presumed WTO-inconsistent? Or, should the conclusion be that the US and Canadian measures of suspension of obligations shall not be presumed to be inconsistent with the DSU? Please elaborate on why one specific conclusion is preferable than the other in your view.

44. The principle of good faith is not relevant to the allocation of the burden of proof in this dispute. The application of this principle therefore does not create a presumption in favour of either party.

45. In repeatedly raising the issue of good faith, the EC has confused the issues by suggesting that to deny it a presumption of compliance in these circumstances would be tantamount to a presumption that the EC has acted in bad faith. Canada does not argue that the EC has acted in bad faith, nor even that it should be presumed not to comply.

46. Rather, the allocation of the burden of proof in this dispute is determined by the existence of the multilateral authorization and the existence of Canada's measure taken on the basis of that authorization. That is, the EC cannot benefit from a presumption of compliance – such that it would be presumed to have satisfied one of the conditions of Article 22.8 – for the simple reason that allowing such a presumption would have the consequence of automatically rendering WTO inconsistent a measure of another Member that was and remains authorized by the DSB. Since the EC is in a state of non-compliance in the *EC – Hormones* dispute, it bears the burden of confirming multilaterally that it has now complied in order to have the authorization terminated.

Q62. Do you agree with the view that (i) if an original complaining party initiates an Article 21.5 dispute challenging the consistency of an implementing measure, that party shall bear the burden to prove that the implementing measure is WTO-inconsistent during the compliance procedure, and that (ii) if an original defending party initiates an Article 21.5 dispute claiming the WTO-consistency of its measure, that original defending party shall bear the burden of establishing the consistency of its implementing measure as a complaining party to the Article 21.5 dispute? Please elaborate on your response.

47. Yes, Canada agrees with the statements in the question.

48. If the original responding party initiates the proceeding under DSU Article 21.5, it bears the burden of demonstrating that its measure is compliant with the recommendations and rulings of the DSB. Since the objective of the proceeding under DSU Article 21.5 is to achieve conformity with all provisions of the covered agreements, it would then be open to any other WTO Member that participates in such proceedings to demonstrate that the measure at issue is not consistent with other provisions of the covered agreements.

49. If the proceeding under DSU Article 21.5 is initiated by the original complaining party, it would bear the burden of demonstrating that the implementing measure is inconsistent with any provisions in any of the covered agreements. It is established case law that panels acting under DSU Article 21.5 may deal with all issues of consistency of the measure concerned with the covered agreements. The Appellate Body in *Canada – Aircraft (Article 21.5 – Brazil)* confirmed this.[6]

Q63. Would the parties consider that the principle *rebus sic stantibus*, could apply to a decision of the DSB (see, *inter alia*, para. 26 of Canada's oral presentation regarding the legal status of DSB decisions)? In its oral comments on Canada's oral presentation, the EC stated that there is no hierarchy in customary international law, the principle of good faith in this case, and a treaty language, the DSB authorization in the current dispute. Could the parties provide evidence that the EC statement is or is not supported by international jurisprudence?

50. Regardless of whether the principle of *rebus sic stantibus* (*i.e.*, fundamental change in circumstances) applies to decisions of the DSB as a general matter, the conditions for it to be invoked successfully in these circumstances are not present.

[6] See *Canada – Aircraft (Article 21.5 – Brazil)*, at para. 41. See also *Australia – Measures Affecting the Importation of Salmon – Recourse to Article 21.5 of the DSU by Canada*, Report of the Panel, WT/DS18/RW, adopted March 20, 2000; and *European Communities – Regime for the Importation, Sale and Distribution of Bananas – Recourse to Article 21.5 by Ecuador*, Report of the Panel, WT/DS27/RW/ECU, adopted May 6, 1999.

51. The EC has not itself invoked the principle to argue that the DSB authorization is no longer in effect. Moreover, even if the EC were to invoke the principle, it could not do so successfully. One of the cumulative conditions codified in Article 62 of the *Vienna Convention on the Law of Treaties* is that the circumstances that are said to have fundamentally changed must have been "unforeseen" at the time the agreement was made (in this case, the adoption of the DSB authorization). At the time WTO Members, acting through the DSB, authorized Canada to suspend concessions, it could hardly be considered unforeseen that the EC would adopt a measure to comply with findings that it was in breach of its obligations under the WTO. On the contrary, the purpose of the authorization to suspend concessions was precisely to induce the EC to adopt such a measure. Therefore, far from being unforeseen, it was expected that the EC would adopt an implementing measure.

52. With respect to the relationship between treaty law and customary international law, the EC has initiated an unnecessary discussion of the hierarchy between sources of international law. The point made by Canada on which the EC was commenting did not depend on resolving issues of hierarchy between sources of international law. Canada has argued that its authorization from the DSB to suspend concessions (specifically granted by treaty) prevails over any claim by the EC to a presumption of compliance.[7] Canada does not argue that there is a conflict, the resolution of which requires the Panel to determine a hierarchy. It is simply that a presumption of compliance does not apply to the EC measure in these circumstances as a result of the DSB surveillance regime. See also Canada's answer to question 61 above.

53. In any event, even if the Panel were to find that there is a conflict between these principles in these circumstances, it could resolve this conflict with reference to the specific principle of treaty interpretation of *lex specialis derogat legi generali*, which provides that specific treaty rules (*i.e.*, those governing the DSB authorization) will prevail over general rules of customary international law (*i.e.*, those providing for a general presumption of compliance).[8] The relationship between the DSB authorization and the EC's claim to a presumption of compliance could also be decided with reference to specific provisions of the DSU. Articles 3.2 and 19.2 of the DSU both provide that panels cannot add to or change the rights and obligations of WTO Members in the resolution of disputes. If the Panel were to find in favour of the EC's arguments – by finding that the EC has satisfied the conditions of Article 22.8 on the basis of this presumption – it would alter Canada's rights under the DSU. Such a decision would alter Canada's rights not only by depriving Canada of the legal basis on which its measure is based but, more importantly, would do so without having the issue of whether the conditions of Article 22.8 have been satisfied confirmed by the DSB.

Q64. If the Panel were not able to reach a conclusion on the first claim of the European Communities under DSU Article 23, do you think the Panel should proceed to examine the second claim of violation of Article 22.8 of the DSU?

54. Canada is not in a situation covered by Article 23 of the DSU because it is not seeking the redress of an alleged WTO violation. Therefore, the examination by the Panel of the status of the DSB authorization for the purposes of the EC's claims under Article 22.8 of the DSU remains the fundamental issue to be determined in this dispute.

Q65. Canada and the United States have argued that the EC measure taken to comply with the recommendations and rulings of the DSB in the Hormones case are incompatible with

[7] For Canada's comments on the EC's efforts to confuse the "presumption of compliance" and the "principle of good faith", see Canada's answer to question 61 from the Panel.

[8] See, for example, Malcolm N. Shaw, *International Law*, 5th ed. (Cambridge: Cambridge University Press, 2003), at 116 [Exhibit CDA-24]. See also *EC Measures Concerning Meat and Meat Products (Hormones)*, Report of the Appellate Body, WT/DS26/AB/R, WT/DS48/AB/R, adopted February 13, 1998, at para. 124.

Article 5.1 and 5.7 of the SPS Agreement. However, the European Communities does not make any reference to these provisions, either in its request for establishment of the panel, or in its first written submission. Do the parties believe that the Panel has, nonetheless, jurisdiction to review the compatibility of the EC implementing measure with Articles 3.3, 5.1 and 5.7 of the SPS Agreement? On what legal basis should the Panel consider itself entitled/not entitled to address the arguments of Canada and the United States in relation to the SPS Agreement?

55. The Panel has jurisdiction to review the consistency of the EC's new measure with Articles 3.3, 5.1 and 5.7 of the *SPS Agreement*. The EC alleges that Canada has acted inconsistently with Article 22.8 of the DSU by maintaining its suspension of concessions despite the EC's "removal" of its offending measure. There is no presumption of compliance that operates in favour of the EC in this case. In the alternative, if a presumption exists, that presumption is rebuttable. In either case, the Panel's determination that the EC has actually "removed" its offending measure (in other words, that it has actually brought its measure into compliance with the recommendations and rulings of the DSB) is a prerequisite to any finding that Canada has breached Article 22.8 of the DSU by maintaining its suspension of concessions. Thus, because the recommendations and rulings of the DSB require that the EC base its measure on a risk assessment as required by Articles 3.3 and 5.1 of the *SPS Agreement*, the Panel has jurisdiction to examine the consistency of the EC's measure with these and related provisions of the *SPS Agreement*.

56. As to the consistency of the EC's measure with Article 5.7 of the *SPS Agreement*, the EC is claiming that it cannot perform a risk assessment on five of the six hormones in question because there is insufficient scientific evidence to do so. The EC thus bears the burden of justifying its "provisional" measure on the basis of the exemption contained in Article 5.7 of the *SPS Agreement*. Consequently, in the context of determining whether the EC's new measure complies with the recommendations and rulings of the DSB, the Panel has jurisdiction to determine whether the EC is able to justify its provisional measure on the basis of Article 5.7 of the *SPS Agreement*.

57. Finally, in the light of the EC's alternative argument in Part II of its First Written Submission, in which it claims that its new measure is "fully compliant with the recommendations and rulings of the DSB", this Panel has full jurisdiction to examine the actual consistency of the EC's measure with the relevant provisions of the *SPS Agreement*. In this regard, we draw the Panel's attention to paragraphs 137 to 147 of the EC's First Written Submission, which set out its claims of compliance with the recommendations and rulings of the DSB.

Q66. In this particular case, would it be for the European Communities to prove the compatibility of its measure with Article 5.7 of the SPS Agreement because it applies certain aspects of that measure provisionally or would it be for Canada and the United States to demonstrate a violation of Article 5.7 because they consider that the EC measure is in breach of that provision? Could the parties discuss the application of the burden of proof in relation to Article 5.7 in light of the panels and Appellate Body findings with respect to that provision in *Japan – Agricultural Products II* and *Japan – Apples*?

58. As the Appellate Body has explicitly noted in *Japan – Agricultural Products II*, Article 5.7 "operates as a *qualified* exemption from the obligation under Article 2.2 not to maintain SPS measures without sufficient scientific evidence".[9] This means that Article 5.7 enables WTO Members, in certain, limited circumstances, to adopt and maintain SPS measures despite the fact that they are not supported by sufficient scientific evidence. Article 5.7 does not exist as an option that can be freely

[9] See *Japan – Measures Affecting Agricultural Products*, Report of the Appellate Body, WT/DS76/AB/R, adopted March 19, 1999, at para. 80 [emphasis in original] [*Japan – Agricultural Products II*].

chosen by the Member concerned in place of Article 2.2. It plays a role as a temporary "safety valve" in situations where some evidence of a risk exists but not enough to complete a full risk assessment, thus making it impossible to meet the more rigorous standards set by Articles 2.2 and 5.1.

59. In the present case, it is the EC that is alleging that there is insufficient scientific evidence to conduct an adequate risk assessment in respect of five of the six hormones at issue. Therefore, it is the EC, as the WTO Member invoking Article 5.7 to justify its provisional measure, that bears the burden of making a *prima facie* case in support of its position. For example, in *Japan – Apples* the panel assigned the burden of proof to Japan to demonstrate that the four cumulative requirements of Article 5.7 had been met.[10] In the present case, Canada has submitted evidence and arguments to demonstrate that the EC has not met its burden and that, in any event, it would be unable to meet this burden.

Q67. Do the parties consider that Article 5.7 applies only when no risk assessment can be made at all or also when scientific evidence exists but is insufficiently specific?

60. The Appellate Body in *Japan – Apples* found that "relevant scientific evidence" will be "insufficient" when the scientific evidence available does not allow, in quantitative or qualitative terms, the performance of a risk assessment as required under Article 5.1 of the *SPS Agreement*.[11] Consequently, Article 5.7 applies when "no risk assessment can be made at all" either because there is simply not enough evidence to conduct a risk assessment, or when the evidence available is insufficiently specific to conduct a risk assessment as defined in Annex A of the *SPS Agreement*.

Q68. Do all parties agree that the term "on the basis" in Article 5.7 of the SPS Agreement has the same meaning as "on the basis" in Article 5.1, i.e. that a "rational relationship" is required?

61. The requirement that a Member adopt a measure "on the basis" of available pertinent information under Article 5.7 is similar to the obligation under Article 5.1 that a Member's SPS measure be "based on" a risk assessment. In other words, in both instances there must be a "rational relationship" between the measure at issue and, in the case of a measure adopted under Article 5.7, the "available pertinent information" and, in the case of any other measure not captured by Article 3.2 of the *SPS Agreement*, the risk assessment. This interpretation is consistent with the need for SPS measures to be based on science as set out in Article 2.2 of the *SPS Agreement*.

Q69. During the *EC – Hormones* proceedings, the European Communities was of the view that "the scientific evidence concerning the need to regulate the use of hormones was in itself sufficient to justify its legislation and the European Communities did not need to rely on the exception provided for in Article 5.7 concerning cases where relevant scientific evidence was insufficient" (DS26/R/USA, para.4.239). Does this mean that "the evidence concerning the need to regulate the use of hormones generally" is different from the specific evidence concerning the health risk associated with the administration of hormones in animals for growth promotion purpose? Is there sufficient evidence concerning the latter?

62. There is a difference in "the evidence concerning the need to regulate the use of hormones generally" in veterinary medicine and the specific evidence concerning the health risk associated with the administration of hormones in animals for growth-promotion purposes. In particular, the exposure data needed to evaluate hormones used for growth-promotion purposes would have to be use specific. Canada considers that a "risk assessment" of a veterinary drug is designed to address a specific use of

[10] See *Japan – Measures Affecting the Importation of Apples*, Report of the Panel, WT/DS245/R, adopted December 10, 2003, at para. 8.212.

[11] See *Japan – Measures Affecting the Importation of Apples*, Report of the Appellate Body, WT/DS245/AB/R, adopted December 10, 2003, at para. 179.

the drug. Therefore, in the case of use of these hormones for growth-promotion purposes, the hormone residue data used to estimate the dietary hormone intake from growth-promotion use would need to be generated specifically, as would the residue data from the use of these hormones for any therapeutic purpose. In this case, there is sufficient scientific evidence to conduct a risk assessment in respect of all six hormonal growth promotants in question. This conclusion is supported by regulatory decisions in many countries and by the fact that JECFA has allocated ADIs (acceptable daily intake) for all six hormones at issue.

Q70. Having regard to the statement of the United States in paragraphs. 151-152 of the first US written submission, the Panel notes that Article 5.7 of the SPS Agreement talks about "available pertinent information" on the health risk. In the parties' views, does this mean that the "available pertinent information" under the circumstances of the current disputes refer to the information on risks associated with the consumption of meat from animals treated with hormones for growth promotion purposes according to good veterinary practice? Or, does it refer to the risk of the five hormones to human health generally?

63. The "available pertinent information" on oestradiol 17β and the other five hormones is adequate to conduct a risk assessment on the use of oestradiol 17β and the other five hormones when used for growth promotion according to good veterinary practices. However, the use of any of these hormones for purposes other than growth promotion (according to good veterinary practices) would require specific risk assessments and the "available pertinent information" would have to be assessed as such.

Q71. Article 5.7 of the SPS Agreement requires that a Member review the measure within a reasonable period of time. In the parties' view, how long should this reasonable period of time be in this case? At which point of time should the calculation of the reasonable period of time start? Has the European Communities conducted such a review after the adoption of Directive 2003/74/EC in September 2003? What is the plan of the European Communities to conduct such review?

64. With regard to the requirement under the second sentence of Article 5.7 of the *SPS Agreement* that a Member review its provisional measure within a reasonable period of time, the Appellate Body in *Japan – Agricultural Products II* found that the reasonable period of time should be assessed on a case-by-case basis and depends on (1) the specific circumstances of each case and (2) the characteristics of the SPS measure at issue.[12] In the case of a total import ban like the one currently facing Canada and the United States, which has the most trade-distorting effect possible, the reasonable period of time should not be construed so as to prolong unnecessarily the trade impact of the provisional measure. The second sentence of Article 5.7 imposes a stringent burden on Members to make active and ongoing efforts to gather and review additional information necessary for a risk assessment. Consequently, from the moment that the measure is adopted, the Member should be acting with diligence to fulfill this substantive requirement of Article 5.7 of the *SPS Agreement*.

Q72. Please explain what you understand to be the relationship between Article 3.1 and Article 5.7 of the SPS Agreement?

65. Consistent with the goal of the *SPS Agreement* to harmonize SPS measures, Article 3.1 sets out the basic obligation of Members to base their measures on international standards except as otherwise provided for in the Agreement. In a case where a Member wishes to introduce a measure with a higher level of SPS protection than that of the relevant international standard, it must do so on the basis of a risk assessment. Article 5.7 allows Members to adopt provisional measures in a situation

[12] See *Japan – Agricultural Products II*, at para. 93.

where there is insufficient scientific evidence to conduct such a risk assessment. However, it does not give Members *carte blanche* in this area. The provisional measure must be based on "available pertinent information", including that from relevant international organizations and measures of other WTO Members. Where a relevant international organization has adopted standards on a particular SPS issue, it makes it extremely difficult for a Member to argue that there is insufficient scientific evidence to conduct a risk assessment, because the existence of an international standard implies that sufficient scientific evidence exists to complete a risk assessment. The burden rests with the EC in this case to demonstrate that, despite the adoption of international standards by Codex regarding the hormones at issue, the scientific evidence is insufficient to allow it to conduct a risk assessment.

Q73. Do you consider it possible that scientific evidence may be judged to be sufficient to undertake a risk assessment at a particular point in time, and yet considered to be insufficient for the same purpose several years later? Does the fact that a significant number of scientific studies have been undertaken with regard to these potential risks in the intervening years have any relevance for your response? Does the existence of international standards have any relevance? Please explain?

66. Yes, it is theoretically possible that scientific evidence judged to be sufficient to undertake a risk assessment at a particular point in time may be considered to be insufficient to conduct a risk assessment for the same purpose several years later. For example, this could be due to a change in the basic understanding of a biological event that is triggered by the chemical under assessment, new scientific data that identify new adverse effects or adverse effects at lower exposure levels. New sources of exposure could also trigger the need to reassess the adequacy of the risk assessment.

67. It would not be the number of scientific studies conducted in the intervening years that would determine whether a new risk assessment was necessary but rather the nature of the studies. For example, if new residue studies (*i.e.*, an analysis of the chemical and significant metabolites in food) were carried out then this would require minimally an exposure reassessment and possibly a risk characterization reassessment. If studies addressed biological endpoints that had not been previously addressed (*e.g.*, the immune system), used new study protocols or more sensitive methodologies, a new hazard identification assessment would be in order.

68. Furthermore, it would be essential to take international standards into consideration. More important than the numerical standard is the basis, support or risk assessment for that international standard. For example, it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues.

Q74. Assuming the Panel deems it necessary to determine whether the European Communities revised measure complies with certain provisions of the SPS Agreement, do the parties consider that the consultation of scientific experts would be necessary or only useful? What would be the issues on which experts should be consulted? To the extent feasible, should the Panel consult the experts consulted in the *EC – Hormones* case?

69. If the Panel deems it necessary to consider whether the EC's revised measure complies with the *SPS Agreement*, the complexity of the issues in this case would require consultation with scientific experts. Were the Panel to so decide, those experts should be consulted as to (1) whether the Opinions and/or studies relied on by the EC constitute the necessary risk assessment identifying the risks to consumers that flow from the ingestion of meat from animals treated with oestradiol 17β; (2) whether there is sufficient scientific evidence regarding the other five hormonal growth promotants at issue to enable the EC to conduct a risk assessment; and (3) whether current scientific knowledge warrants the EC's ongoing ban regarding the six hormonal growth promotants.

70. If the Panel decides to consult experts, those experts who advised the panel in the original *EC – Hormones* case should be among the candidates. However, Canada may wish to propose several other recognized experts as candidates.

ANNEX B–3

REPLIES OF CANADA TO QUESTIONS POSED BY THE EUROPEAN COMMUNITIES AFTER THE FIRST SUBSTANTIVE MEETING

(3 October 2005)

Questions to the United States and Canada:

Q1. According to the United States and Canada the continued suspension of concessions and related obligations is based on the original DSB authorization and not on the (alleged) WTO-inconsistency of the EC's compliance measure. Does this mean that the United States and Canada claim a right to continue the application of sanctions even if the EC measure is WTO-consistent as long as the DSB authorization has not been formally withdrawn?

1. Canada would not claim a right to suspend concessions in circumstances where there has been multilateral confirmation that a measure taken to comply with recommendations and rulings of the DSB actually does comply. Multilateral confirmation of this compliance would come in the form of the adoption by the DSB of findings and recommendations of a WTO dispute settlement panel and/or the Appellate Body. The adoption of such findings by the DSB would at the same time be sufficient to constitute revocation of the DSB authorization, whether implicit or explicit.

Q2. You argue that the DSB authorization to suspend concessions can only be revoked following a multilateral determination of compliance of the EC's implementing measure. You suggest that this could be achieved, inter alia, through an Article 21.5 procedure initiated by the European Communities. In such a case would the European Communities be the "complaining party" within the meaning of Article 6? Who would be the "defending party"? What would be "the specific measures at issue"? What would be the legal basis for the "complaint"? What would the European Communities be complaining against?

2. See Canada's answer to questions 45 and 62 from the Panel**.**

Q3. Would the United States and Canada participate in a self-initiated Article 21.5 proceeding, such a proceeding? If yes, would they do so because of a legal obligation?

3. Yes. Regardless of whether there is a legal obligation to participate, it would be in Canada's interest to participate if the EC initiated a proceeding under DSU Article 21.5 to obtain confirmation of the compliance of its measure with the recommendations and rulings of the DSB in *EC – Hormones.*

Q4. What would be the terms of reference of a self-initiated Article 21.5 proceeding? Would the European Communities be required to anticipate any possible claims by the United States and Canada? Could the United States and Canada raise new claims outside the legal basis for the "EC complaints"? If yes, how could this be squared with the terms of reference?

4. See Canada's answers to questions 45 and 62 from the Panel.

Q5. In the oral hearing, Canada submitted that under an Article 21.5 proceeding it would not only be possible to review the compliance measure but also the legality of the continued application of the sanctions? According to Canada, is the continued application of the

suspension of obligations therefore a measure which can be reviewed under Article 21.5? What are the US' views on this suggestion?

5. No, the measure suspending concessions *per se* would not be reviewed by an Article 21.5 panel. However, if a panel established under Article 21.5 confirmed the compliance of an implementing measure, it could recommend that the DSB authorization be terminated. See Canada's answer to question 7 below.

Q6. In the oral hearing, the United States argued that there is no "disagreement" between the United States and the European Communities as to the WTO-consistency of the new compliance measure. If this is correct, how could the European Communities self-initiate an Article 21.5 proceeding as suggested by the United States?

Q7. Assuming that a proceeding under Article 21.5 comes to the conclusion that the EC's compliance measure is WTO-consistent. How would this lead to a withdrawal of the DSB authorization? What would be the legal basis for the DSB to "withdraw" the authorization, and what decision-making mechanism would apply for that DSB action.

6. A finding in a proceeding under Article 21.5 that a measure taken by the EC to comply is WTO consistent would lead to a withdrawal of the DSB authorization by the adoption by the DSB of the panel's findings confirming compliance. See Canada's answer to question 55 from the Panel.

7. Although Canada does not see it as necessary, if the EC were concerned about the effect of such findings on the ongoing validity of the DSB authorization, it could also cite Article 22.8 of the DSU in its request for the establishment of the panel under Article 21.5. There would then be no doubt as to whether the panel could make recommendations that the DSB authorization is no longer in effect. See also Canada's answer to question 8 below.

Q8. Canada argued in its First Written Submission that as the outcome of a new proceeding "the result would be a recommendation to the DSB to terminate the DSB authorization" (para. 47)? How can this statement be reconciled with Article 19 DSU whereby the Panel or Appellate Body only issues recommendations to the "Member concerned" but not to the DSB? What does the United States think?

8. Article 19 of the DSU simply sets out what panels shall do with respect to recommendations to Members to bring themselves into compliance. Nothing in that provision prevents panels from recommending to the DSB that the authorization be terminated.

Q9. How is the theory of the "withdrawal of the DSB authorization" in line with the text of Article 22.8, first sentence, of the DSU, and what is the need for it in the light of that provision?

9. The formal "withdrawal of the DSB authorization" is not required by the dispute surveillance regime set up by the DSU. Rather, it is the confirmation by the DSB of the EC's compliance that is required for the DSB authorization no longer to be available to Canada. See Canada's answer to question 55 from the Panel.

Q10. Is it Canada' opinion that the DSB authorization which it received in the Brazil – Aircraft case (WT/DS46) is (implicitly?) revoked after the Panel under the second Article 21.5 proceeding found that Brazil' compliance measure was WTO-consistent? What are the United States' views on this issue?

10. The premise of the EC's question is in error.

11. Although the panel ruled, in *Brazil – Aircraft (Article 21.5 – Canada II)*, that Brazil's program PROEX III as such was not inconsistent with the *SCM Agreement*,[1] PROEX III did not withdraw PROEX I and PROEX II, nor any subsidies issued under these programs. PROEX I and PROEX II were programs that had previously been found inconsistent with the *SCM Agreement*. Thus there is no basis for any suggestion on the part of the EC that Canada's authorization to suspend concessions to Brazil was implicitly terminated.

Q11. Canada argues that it has not violated Article 21.5 because the EC's could have initiated a compliance Panel itself (para. 76). Could Canada please explain how such a possibility for the European Communities affects Canada's obligations under Article 23.1 and 21.5 of the DSU?

12. The EC mischaracterizes Canada's arguments in paragraph 76. Canada's argument that it has not violated Article 21.5 does not depend upon the fact that the EC could have initiated proceedings under Article 21.5.

Q12. According to the United States and Canada the continued imposition of sanctions is justified because of the DSB authorization. Assuming the European Communities would try to seek a revocation of the DSB authorization based on a new case under Article 22.8, how could such a proceeding result in a Panel finding that the sanctions are illegal (implying according to the United States and Canada that the DSB authorization would end) if at the same time the Panel accepts the US' and Canada's theory that due to the DSB authorization the sanctions are per se WTO consistent?

13. Proceedings under Article 22.8 of the DSU would, as Canada argues these proceedings should, include as an initial issue the confirmation of the compliance of the underlying measure claimed to have been removed, prior to any finding on the ongoing authorization of the suspension of concessions. If a panel confirms the actual compliance of the measure taken to comply, it would make recommendations that the DSB authorization should be terminated and, further, make recommendations that Canada remove its suspension of concessions. See Canada's answer to question 55 from the Panel.

Q13. The United States and Canada accept that the purpose of suspension of concessions is to rebalance the rights and obligations of WTO Members and/or to induce compliance. Therefore, would the United States and Canada agree that the purpose of the current continuation of the suspension of concessions is also to rebalance rights and obligations and/or to induce compliance?

14. In the absence of a mutually satisfactory agreement or of multilateral confirmation that the EC's measure now complies with the recommendations and rulings in *EC – Hormones*, and thus has been "removed" within the meaning of DSU Article 22.8, the suspension of concessions continues to serve the purpose(s) for which the authorization to suspend concessions was originally granted by the DSB to Canada.

Q14. In its First Written Submission, Canada states that the European Communities is still today under an ongoing obligation to comply despite its implementing measure (para. 40). Does the United States agree? If the European Communities are still under an obligation to comply is it correct to assume that the United States and Canada consider the EC's compliance measure as WTO-inconsistent?

[1] *Brazil – Export Financing Programme for Aircraft: Second Recourse by Canada to Article 21.5 of the DSU*, Report of the Panel, WT/DS46/RW2, adopted August 23, 2001, at para. 6.1.

15. The fact that the EC has adopted a measure that it alleges complies with the recommendations and rulings of the DSB in the *EC – Hormones* dispute is not, in and of itself, determinative of the actual compliance of that measure. If the EC wishes to have Canada's DSB authorization terminated, it must do more than simply adopt a new measure and then assert compliance. In the absence of a mutually satisfactory solution, the EC must obtain multilateral confirmation that its measure complies with the recommendations and rulings of the DSB in *EC – Hormones*.

Q15. How does such a conclusion affect the US' and Canada's allegation that they have not yet made a "determination" as to the WTO-inconsistency of the EC's compliance measure?

16. See Canada's answer to question 57 from the Panel. See also Canada's answers to questions 43, 44 and 48 from the Panel.

Q16. Do Canada and the United States consider that it is at all possible to make a "determination" in the present situation given that they are acting under a DSB authorization? If you do, could you give an example of what would constitute a "determination" in your view?

17. Canada's continued reliance on the DSB authorization for its suspension of concessions to the EC is not a "determination" regarding the EC's new measure within the meaning of Article 23.2(a) of the DSU. See Canada's answer to question 57 from the Panel. See also Canada's answers to questions 43, 44 and 48 from the Panel.

Q17. What is a reasonable timeframe for developing a view on the WTO-consistency of the EC's compliance measure in the present case in the light of the continued application of sanctions against the European Communities?

18. In the absence of a mutually satisfactory solution, it is in the discretion of the EC, if it wishes to have the DSB's authorization to suspend concessions terminated, to obtain multilateral confirmation of the compliance of its new measure with the recommendations and rulings of the DSB.

Q18. In its First Written Submission Canada refers to an "[abuse of] its right to implement" in case of a scam measure (para. 45) Is it Canada's view that the EC's compliance act is a "scam measure"? What is the US' view?

19. Canada has not argued that the EC measure is a "scam measure". In fact, the issue is not whether the EC measure is a "scam measure"; the issue is whether the EC measure complies with the recommendations and rulings in *EC – Hormones*.

Q19. What is the textual basis in the WTO Agreement for a reversal of the burden of proof in a "post-implementation" scenario (Canada's First Written Submission, paras. 56 to 58), and how does this theory of the reversal of the burden of proof fit with the WTO jurisprudence? Does the United States agree with Canada's theory?

20. Paragraphs 56 to 58 of Canada's First Written Submission do not present a theory of the reversal of the burden of proof. In those paragraphs, Canada argues that the EC is not entitled to rely on a presumption of compliance such that it has automatically satisfied one of the conditions of Article 22.8 of the DSU. As a result of the specific authorization of Canada's suspension of concessions, and in the light of the EC's obligation to comply with the recommendations and rulings in *EC – Hormones*, the EC now bears the burden of demonstrating that it has done so. See Canada's answer to question 61 from the Panel.

Q20. During the Oral hearing the United States submitted that the EC's approach in the FSC-case was "appropriate". Why does the United States believe that the same approach is not

"appropriate" in the present case where the United States is continuing sanctions despite an EC's compliance measure?

WORLD TRADE ORGANIZATION

WT/DS321/R/Add.3
31 March 2008

(08-0910)

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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex C to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex B: Add.2
- Annex D: Add.4
- Annex E: Add.5
- Annex F: Add.6
- Annex G: Add.7

ANNEX C

REPLIES OF THE PARTIES TO QUESTIONS POSED BY THE PANEL AND OTHER PARTIES AFTER THE SECOND SUBSTANTIVE MEETING AND COMMENTS BY THE PARTIES ON THE OTHER PARTIES' REPLIES

ANNEX C–1

REPLIES OF THE EUROPEAN COMMUNITIES TO QUESTIONS POSED BY THE PANEL AFTER THE SECOND SUBSTANTIVE MEETING

(18 October 2006)

Questions to all parties

Q1. With reference to the statement by the European Communities, *inter alia* in para. 12 of the EC reply to Question 3 of the United States, do the parties consider that a Panel is entitled to address "systemic claims" or issues related to "systemic obligations" and, if so, to what extent?

1. By "systemic claims" and "systemic obligations" the European Communities is referring to obligations contained in the DSU that are related to the WTO dispute settlement mechanism as a system, are procedural in nature and independent of substantive obligations contained in other WTO agreements. A failure to bring a case under Article 21.5 is a violation of a procedural obligation, irrespective of what the underlying disagreement on the question of compliance is about. Equally, from the European Communities' point of view, the continued application of sanctions in the face of presumed compliance and in the absence of a compliance review constitutes a violation of a procedural nature, irrespective of the substantive requirements of actual compliance.

2. The Panel is not only entitled, but has an obligation to rule on claims of violation of such obligations under the DSU, which have been properly made by the European Communities in this dispute. The European Communities further notes that several Panels in the past have already ruled on Article 23 claims.[1]

Q2. With reference to the US rebuttal, para. 27, do the parties consider that a measure that does not comply with the requirements of Article 5.7 SPS would automatically be in breach of Article 2.2 SPS, or Article 5.1 SPS, or both?

3. In the European Communities' view this question may be based on a misunderstanding of the point made in para. 27 of the US Rebuttal Submission. The United States is not arguing that a failure to meet the requirements of Article 5.7 automatically results in a violation of Articles 2.2 and/or 5.1. Rather the US is arguing that a measure has to satisfy the obligations under Articles 2.2 and 5.1 if the conditions of Article 5.7 do not apply.

4. Indeed, assuming that a failure to meet the requirements of Article 5.7 would automatically lead to a violation of Articles 2.2, 5.1 or both, would lead to absurd results. Picture a measure that is based on a risk assessment within the meaning of Article 5.1. That measure would not fulfil the conditions of Article 5.7, as it is not provisional in nature, is not based on "available pertinent information," has not been followed up through further research etc. Nevertheless, the measure is of course perfectly in compliance both with Articles 2.2 and 5.1.

5. At the same time, there is no doubt that if a measure that was thought to fulfil the requirements of Article 2.2. and 5.1-5.2 is found a Panel not to do so, it should be considered whether it fulfils the requirements of Article 5.7, in view of the lower amount of pertinent scientific evidence and the greater role which scientific uncertainties play in the adoption of an Article 5.7 measure. As the European Communities has argued in its reply to Question 66 of the Panel, Article 5.7 is a special

[1] See only *US – Certain EC Products*, *US – Section 301*; *EC – Vessels* ("Shipbuilding Subsidies").

regime in relation to Article 5.1. It applies to provisional measures adopted in the face of insufficient scientific evidence and is in that sense also identified as *lex specialis* to Article 2.2.

Q3. When and how was each of the following documents made available to Canada and the United States? Please answer independently for each of the documents mentioned below:

(i) 1999 Opinion;
(ii) 2000 Opinion;
(iii) 2002 Opinion;
(iv) each of the "17 studies".

6. The European Communities has replied to this question in detail in its reply to Question 16 of the Panel (see paras. 79ff) and in paras. 111ff of its Second Written Submission.

7. The 1999 Opinion was adopted on 30 April 1999 and put on the internet almost immediately thereafter, and was transmitted to the US and Canada. In bilateral contacts, both US and Canadian counterparts were made aware of this fact. As explained in para. 96 of its Oral Statement at the first substantive meeting as well as in para. 112 of its Second Written Submission, a meeting between EC and US scientists was arranged in Washington in June 1999 to discuss the results of the 1999 Opinion. No such meeting took place, however, between Canadian and EC scientists, as none was requested by Canada.

8. The 2000 Opinion was adopted on 3 May 2000 and put on the internet very shortly thereafter. In informal bilateral contacts, both US and Canadian counterparts were also made aware of this fact.

9. On 3 November 2000 the EC draft legislation was notified to the SPS Committee (G/SPS/N/EEC/102). The notification (revised version submitted on 17 November 2000, see G/SPS/N/EEC/102/Rev.1), in point 12, refers both to the 1999 and the 2000 Opinion and provides the internet link where the Opinions can be accessed. Canada submitted its comments on this notification in December 2000 (see EC-Exhibit 64) in which it stated that Canadian officials at Health Canada had reviewed the Opinions, so clearly Canada must have had access to them.

10. The 2002 SCVPH's third assessment had been long announced before it was actually carried out. The European Communities had made public the fact that it had launched 17 studies, the results of which would be reviewed in time.[2] The 2002 Opinion, whose sole purpose was to review all the available evidence and in particular the results of the 17 studies, was adopted on 10 April 2002 and put on the internet shortly thereafter. In bilateral contacts, both US and Canadian counterparts were made aware of this fact and actually have never complained that they had not received it.

11. The preliminary findings from 17 scientific studies had already been taken into account in the 1999 SCVPH opinion, as they were available at the time. The final results from the studies were taken into account and were cited and referenced in the 2002 Opinion (page 28). At the time of the adoption of the 2002 Opinion, only one study had not yet been published (that is Exhibit EC-29), whilst one study was from the start not meant for publication (Exhibit EC-7), as it contained the samples of meat collected from the US supermarkets that was sent for analysis in the European laboratories. Also one other study (Exhibit EC-30) was partly published in Lange I.G., Daxenberger A., Meyer H.H., Rajpert-De Meyts E., Skakkebaek N.E., Veeramachaneni D.N.: Related Articles, Links Abstract Quantitative assessment of foetal exposure to trenbolone acetate, zeranol and melengestrol acetate, following maternal dosing in rabbits. Xenobiotica. 2002 Aug; 32 (8):641-51. But in view of the breadth of its research it continued in collaboration with US scientists after 2002. It appears that its final results have not been published yet. It should also be clarified that

[2] Not least in Codex, see for example 11th session of the CCRVDF.

Exhibit EC-10 was published in AMPHIS 2001, vol. 109, p. 89-95, and it is contained also in Exhibit EC-65, at pages S426-432. It should further be mentioned that some of the scientific experiments in view of their breadth have given rise to more than one publication (see list submitted by EC as Exhibit EC-7 through 42, see also reply to Question 16). It follows that all of the studies, except two, where published and thus were publicly available at or before the 2002 SCVPH Opinion. Moreover, Exhibit EC-65, which is the result of an international scientific conference of May 2001 to which many US scientists including from the US FDA had participated, published again a very large number of the 17 studies. They were thus accessible to the defending parties before 2002.

12. As mentioned in para. 94 of the Second Written Submission, Canada, according to its own statements made on the internet, carried out an "intensive review" of the 17 studies (based on the reference list as annexed to 2002 Opinion), only the conclusion of which is reported on the internet (see footnote 77 at para. 94 for internet address).

Q4. Has the European Communities assessed in a systematic manner the existence and level of risks from failure to observe good veterinary practices with respect to the administration of oestradiol 17β as a growth promoting hormone to cattle, in particular in the United States' and Canada's markets? If so, please indicate where this assessment is to be found in the evidence provided to the Panel.

13. Yes, the European Communities has indeed assessed in a very systematic manner both the existence and the level of risks from failure to observe GVP in the administration not only of oestradiol-17β but also of the other five hormones when used for growth promotion, in particular in the US and Canada. Although it is not clear what the Panel means by "systematic manner", the European Communities has performed this assessment as systematic as it can be and, in any case, in accordance to the indications contained in the 1998 Appellate Body report in the *Hormones* case (at para. 207). There the Appellate Body has said that "systematic analysis" would entail to investigate and evaluate "the actual problems that have arisen at the borders of the European Communities or within the United States, Canada and other countries exporting meat and meat products to the European Communities". The European Communities has already explained the evidence and assessment it has made in some detail with its reply of 3 October 2005 to written questions no 17, 27 and 31 from the Panel.

14. More specifically a regards the **existence of risk**, the European Communities has already referred to the relevant evidence with its reply of 3 October 2005 to question 17 (para. 89) and question 27 (at para. 154). The evidence is contained in Exhibits EC-11, 12, 16, 17, 18, 34, 47, 51B, 52, almost all of which were also published in Exhibit EC-65 (in the form of a book). This evidence has clearly identified and characterised the hazard resulting from the implants that are freely available in the US and the Canadian market. Moreover, please note that most of the experts have confirmed (e.g. Dr. Boisseau) that if GVP is not observed the ADIs and the MRLs proposed by Codex become useless. The experiments described in the Exhibits mentioned above were carried with hormonal implants that are actually licensed for use in the US and Canada and considered both their recommended use and situations of abuse and/or misuse.[3]

15. As regards the **level of the risk**, the European Communities has undertaken specific studies to evaluate the exposure assessment from situations resulting from **real as well as experimental** situations of abuse and/or misuse in the markets of both defending members. Thus, it carried out specific veterinary inspections in the US (Exhibit EC-67) and Canada (Exhibit EC-68), with the agreement of these countries, and has made a specific calculation of the level of the risk for imports coming from both countries in Exhibit EC-73. This assessment of risk is not based on theoretical or

[3] Since oestradiol-17β is present in almost all of the licensed implants in the US and Canada, it is obvious that the evidence mentioned in the above EX Exhibits has also examined oestradiol-17β.

hypothetical assumptions (as the US and Canada wrongly contend), but on examples from realistic conditions of use, taking into account **specific, real and undisputed** instances of abuse and/or misuse that have occurred both in the US (see, e.g., Exhibits EC-53, 67, 69 and 96)[4], and in Canada (see, e.g., Exhibits EC-53, 68 and 70). In addition, the level of risk was further assessed in a specific study that imported in the EC hormone-free and hormone-treated meat sold in the supermarkets in the US (see Exhibit EC-53), and this was further compared with the situation in the EC (see, e.g., Exhibit EC-49). The European Communities submits that a more systematic assessment of realistic conditions of abuse and/or misuse cannot be carried out, and the evidence showed levels of exposure that exceeded the ADIs established by Codex, taking into account the most recent detection methods and the levels of endogenous production by pre-pubertal children. More importantly, the evidence shows beyond doubt that the situations of abuse/or misuse occurring in the US and Canadian market are not exceptional nor occasional.

16. It should finally be stressed that all these pieces of evidence were assessed in the 1999 Opinion (section 3.3, pages 30-32) and the 2002 Opinion (pages 10-12) of the SCVPH and have been taken into account by the risk manager for the adoption of Directive 2003/74/EC. It is noteworthy that the defending members have not really contested this evidence, other than to argue basically that the EC used "unrealistic misuse scenarios" (see, e.g., Canada's 2nd oral statement of 2-3 October 2006, at para. 74; and the US oral statement of 2 October 2006, at para. 60). It is amazing that the US for the first time tries to minimize the health risks from "extra-label use" and sale freely over the counter (*ibid*., at para. 61), which are contradicted by the statements by the US FSIS.[5] Equally surprising is now the attempt by the US to downplay the importance of abuse and/or misuse (*ibid*., at para. 62) arguing that there can be no 100% assurance. The US argues (*ibid*., at para. 64) that "no food safety system is safe", implying that the other WTO members are obliged to accept the failures of the US system despite the risk to human health in the importing country which this kind of failures will inevitably have, as the experts have explained (*e.g.* Dr. Boisseau and Dr. De Brabander). Moreover, the US does not explain why the statements by the US FSIS that " is concerned about the widespread, illegal use of drug implants in young calves that was discovered in 2004", and that "FSIS learned that the use of growth promoting implants was a widespread practice within the veal industry" (and the so many other examples cited in Exhibit EC-73) should not be given the appropriate weight by the EC in its risk assessment.

Q5. In its comments on comments of the United States and Canada on experts replies to the Panel questions (in particular Question 13), the European Communities indicates that oestradiol 17β might be a "weak genotoxin" (para. 44). At what doses is genotoxicity observable *in vivo*? How are these doses comparable to those found in meat from cattle treated with growth promoting hormones? How would this assertion affect the identification of adverse effects and the evaluation of potential occurrence of these effects from consumption of meat from cattle treated with oestradiol 17β for growth promotion purposes?

[4] See Exhibit EC-102 which states, inter alia, that the US Food Safety and Inspection Services (FSIS) "is concerned about the widespread, illegal use of drug implants in young calves that was discovered in 2004".

[5] See above Exhibit EC-102 which states, inter alia, that the US Food Safety and Inspection Services (FSIS) "is concerned about the widespread, illegal use of drug implants in young calves that was discovered in 2004". The same exhibit also states that "FSIS learned that the use of growth promoting implants was a widespread practice within the veal industry. However, the Food and Drug Administration has not approved growth promotion implants for use in food animals presented for slaughter as veal and considers their use to be a violation of the Federal Food, Drug, and Cosmetic Act". This example and so many other that have been identified demonstrate that, contrary to what the US has been arguing before the Panel, abuse and/or misuse is a "widespread practice in the US veal industry". Indeed, it cannot be otherwise as long as these implants are available freely over the counter in both defending countries, and the manufacturers recommend multiple implanting with combinations of these hormones for faster growth of the animals.

17. The question concerns essentially whether oestradiol-17β is mutagen *in vivo*, and, if so, at what dose. The 1999 SCVPH Opinion cites one study of mutagenicity in vivo (at p. 41). With its reply to Panel's Question no 13 to the experts, the European Communities has also provided further – more recent – references to *in vivo* studies.

18. The study by *Cavalieri et al.* (2006) (Exhibit 125) reported that exposure of rats for 20 weeks (140 days) to oestradiol from Silastic capsules, which is a method to release low amounts of a compound over prolonged time periods, led to a statistically significant increase in mutagenesis in the inguinal mammary fat pads. A dose of 5 milligram of estradiol was used, which at first sight seems very high. The precise amount released by the capsules used in the Cavalieri et al. study was not determined.[6] Assuming that the 5 milligrams were completely released within 140 days (which usually is not the case because the dose is designed high enough to secure that the daily exposure is still the same on the last day), a rather conservative estimate based on the published findings would be about 1 microgram per day oestradiol release from the capsules containing 5 mg oestradiol used by Cavalieri, and for a 330 g rat, this would be about a 3 microgram per kilogram per day dose of oestradiol (3000 ng / kg /day). This would mean that the MDD (Maximum Daily Dose) of estradiol in this rat study was at maximum about 35 micrograms[7] or about 0.1 micromole or about 200 micrograms per kilogram body weight.[8]

19. If the daily production rates in pre-pubertal children, according to the original values from the Klein assay were taken into account (0.04 µg/day), the ADI established by JECFA (based on the very high rates of endogenous production of pre-pubertal children of 6.5 µg/day), may be exceeded at most around 1-2 fold, but not by orders of magnitude or "massively" higher, as the defending parties have argued. Moreover, they are still much less than the doses often used in toxicological studies of chemicals, where the lowest doses could be 2-3 orders of magnitude larger than the doses experienced by human consumers.

20. Indeed, JECFA has determined that the maximum oestrogen derived from hormone-treated beef is 84 ng/ person / day that would be for a 60 kg adult 1.4 ng/kg/day. But for a 20 kg child, the amount would be 4.2 ng/kg/day. If so, this would mean that oestradiol had a mutagenic effect at a

[6] Normally such silastic tubes are made to ensure an even release over a long time and to do that there must be a lot left at the end of the experiment (otherwise the dose would decrease during the experiment). On a daily basis this would be: "total amount of estradiol in implant" – "left over at end of experiment" / "days of exposure". Since there are values for how much is left in the hormonal-implants used in cattle at slaughter and given that it is the same principle as silastic tubes in rodents, the %-left-over could be comparable. If so the released amount in the rodents could be calculated. We understand that the underlying study which will provide these data is about to be published: P.C. Mailander, J.L. Meza, S. Higginbotham and D. Chakravarti, Induction of A.T to G.C mutations by erroneous repair of depurinated DNA following estrogen treatment of the mammary gland of ACI rats, J. Steroid Biochem. Mol. Biol., at the November issue, 2006. Moreover, as Dr. Guttenplan has been working with the same scientists in that study, so the Panel may wish to ask him to clarify this information.

[7] This estimate is likely to be on the high side at the end of the study at which point about 40% of the initial dose usually remains in the silastic capsule.

[8] However, from other experiments using similar silastic capsules the dose of oestradiol released from these capsules was reported. From an article published by Ewing et al. in 1979 who used the same Silastic capsules (OD 3.18 mm, ID 1.98 mm) used in the Cavalieri et al. 2006 study, the reported release rate for oestradiol was 2.4 micrograms / cm /day, and according to another paper by Wang and Wong (1998), this would be if there was 25 mg of oestradiol packed into a 1-cm capsule. See Ewing, L.L., R.A. Gorski, R.J. Sbordone, J.V. Tyler, C. Desjardins and B. Robaire (1979): Testosterone-estradiol filled polydimethylsiloxane subdermal implants: effect on fertility and masculine sexual and aggressive behavior of male rats. Biol Reprod 21(4): 765-72; and Wang, Y.Z. and Y.C. Wong (1998). Sex hormone-induced prostatic carcinogenesis in the noble rat: the role of insulin-like growth factor-I (IGF-I) and vascular endothelial growth factor (VEGF) in the development of prostate cancer. Prostate 35(3): 165-77.

dose potentially within the 1000-fold safety margin established from a LOAEL, based on the assumption of a threshold for this effect !

21. With respect to the other in vivo studies mentioned, the European Communities would like to clarify the following. The study in SENCAR mice showing mutagenicity of the 3,4-quinone of E2 (the putative mutagenic metabolite) used a dose of 200 nanomoled, which is about 60 microgram. Again, we do not know for sure how this relates to the daily amount of E2 in the mouse, but an educated guess is that the dose of 60 microgram is probably one or at the most two orders of magnitudes above the endogenous production, and cannot be considered as huge dose either. As for the study on the mutagenicity in the mammary gland of ACI mice is so far available as an abstract only, so there is no much information available.

22. Finally, the study showing the formation of the typical DNA adducts of E2-3,4-quinone in human breast tissue (EC Exhibit 118) did not administer any exogenous E2. So the adducts are formed by the metabolites of the endogenously produced E2 alone.

23. In conclusion, it is very important to understand that the issue of the dose administered is not very crucial for the *in vivo* genotoxicity in the case of oestradiol-17β, and that the defending parties have been trying to confuse the debate on the basis of unscientific and simplistic allegations. Indeed, from the previous comments it appears that the doses used to elicite in vivo mutagenicity are not massively high. Quite the opposite, they seem to fall within the safety margin established by JECFA, which means that the residues in meat from hormone-treated meat are also capable of producing this adverse effect. Moreover, there are many scientists today who rightly believe that setting ADIs and MRLs would not be used for DNA-reactive substances which are both genotoxic and carcinogenic because "it is assumed that there is no exposure without any potential risk, i.e. it is suggested that exposure to even a single molecule could produce DNA damage".[9]

Questions to the European Communities:

Q6. Should the Panel agree with the European Communities' main claim that the United States and Canada have breached Article 23 of DSU read together with Articles 21.5 and 22.8, what would be the consequences of such a conclusion for the United States and Canada? More particularly, would the United States and Canada:

(a) be expected to withdraw the suspensions of concessions or other obligations or suspend their application?

(b) be expected to initiate an Article 21.5 procedure against the EC? or

(c) would they be expected to do both?

(Please note that the Panel is fully aware of its obligations under Article 19 DSU)

24. As explained in paras. 73 et seq. (WT/DS320) as well as in paras. 71 et seq. (WT/DS321) of its first written submission as well as in paras. 94 (WT/DS320) and para. 96 (WT/DS321) the European Communities' position is that Canada and the United States are at least under an obligation to do *either* (a) *or* (b). However, the European Communities considers that it would be appropriate if the United States and Canada did (c).

[9] See S. *Barlow et al*., Risk assessment of substances that are both genotoxic and carcinogenic – Report of an International Conference organised by EFSA and WHO with support of OLSI Europe, Food and Chemical Toxicology, 44 (2006) 1636-1650, at page 1637, available on line at www.sciencedirect.com.

25. In the absence of such a resolution to this dispute, however, there can be no doubt that the United States and Canada are under an obligation to withdraw the suspension of concessions of other obligations or suspend their application, if they do not initiate a 21.5 proceeding.

26. Equally, there can be no doubt that they are under an obligation to initiate a 21.5 proceeding if they continue to disagree on the compliance of the EC implementation measure (manifesting this disagreement through the continued application of the suspension of concessions).

27. In the case of a continued disagreement, as explained elsewhere, the European Communities is furthermore of the view that it would be appropriate for the United States and Canada to both suspend the application of the suspension of concessions *and* initiate 21.5 proceedings. This is what the European Communities has done in the *FSC* case.

28. Of course and ideally, after the thorough debates at the expert meeting, the United States and Canada are free to abandon their disagreement and accept the European Communities implementation measure as compliant. Thus, they would cease the application of the suspension of concessions and there would be no need for a 21.5 proceeding.

Q7. Is the Panel correct in understanding that the European Communities pursues two different "matters" before the Panel:

(a) one regarding the United States' and Canada's unilateral determinations of violation by the European Communities further to its notification of Directive 2003/74/EC; and

(b) one regarding the maintenance of retaliations by the United States and Canada despite actual compliance;

the latter being conditional upon the Panel rejecting the EC claims under the former?

29. The European Communities is not sure to fully understand the meaning of this question.

30. It seems appropriate to first recall the Appellate Body's definition of the "matter" before the DSB:

> [t]he '*matter* referred to the DSB' ... consists of two elements: the specific *measures* at issue and the *legal basis of the complaint* (or the *claims*).[10]

31. On the basis of this definition, there is one single matter here and that is the matter as referred to in the European Communities' request for establishment of a Panel. The request describes several measures and a number of different claims. These claims are further developed in the European Communities' First Written Submission and certain of these claims have been made unconditionally while others are conditional. For the sake of clarity, these unconditional and conditional claims are set out in two different parts, part one addressing claims based on Article 23 read together with Article 21.5 and with Article 22.8, part two addressing a direct violation of Article 22.8. The second part is conditional upon a negative finding on the first part.

32. The above description of two supposedly different "matters" does not reflect the fact of a single matter as just described, nor is it accurate in itself: the issue of a unilateral determination also relates to the maintenance of retaliation as evidenced through the claim based on Article 23 read together with Article 22.8.

[10] AB Report *Guatemala – Cement I*, at para. 72.

33. Furthermore, the European Communities has not generally argued that the "notification" as such is the event that triggers the issue of a unilateral determination (see also para. 44 of its Oral Statement at First Hearing). In the specific circumstances of this case, it seems clear that both the United States and Canada have made such a unilateral determination immediately following the notification. Furthermore, as explained in para. 32 of its Rebuttal Submission the European Communities sees merit in the argument that the time factor may be relevant when for assessing when a "determination" has been made.

Q8. The Panel understands that the European Communities initiated risk assessments with respect to all six hormones at issue (see, e.g., Directive 2003/74/EC, third introductory paragraph).

(a) Could the European Communities confirm, with respect to oestradiol 17β and in light of its statement in para. 192 of its rebuttal and its comments on Question 14 of the Panel to the experts, whether:

(i) it proceeded through the four steps of risk assessment identified by Codex; or

(ii) could have proceeded through the four steps but decided not to do so in light of its findings on genotoxicity of oestradiol 17β?

(b) Could the European Communities confirm, with respect to each of the other five hormones at issue, at what stage(s) of its risk assessment it considered that relevant scientific evidence was insufficient and decided to provisionally ban the importation of meat treated with those hormones on the basis of available pertinent information.

34. **Ad (a).** The European Communities confirms its comments on the Question 14 of the Panel to the experts. As regards the statement in para. 192 of its Rebuttal Submission, the European Communities is grateful to the Panel for pointing out the error and oversight. The error is double because: first, the steps of a risk assessment as defined by Codex are four (not three) and, second, the terminology used in para. 192 to describe the first three of them is not correct either (see following para. 193 where the proper terminology is used for the first three steps). The words used in para. 192 is an isolated oversight and does not reflect the position which the European Communities has expressed in so many other places in its written submissions and the oral hearing. Indeed, with its reply of 3 October 2005 to Written Question No 24 from the Panel, in particular paragraphs 140-143, the European Communities has properly described the four steps of a risk assessment and the reasons for which it thinks it has complied with them in this case. See also paragraphs 145-152 of its reply of 3 October to Written Question No 25 from the Panel. Moreover, a careful examination of the 1999 Opinion shows beyond doubt that the European Communities has completed the four steps, albeit it made a qualitative exposure assessment for the reasons explained therein.

35. **Ad (a), (i) and (ii).** The European Communities has said and repeats that it has performed the four steps in its risk assessment for all these hormones. As regards the third step (exposure assessment), it performed both a quantitative estimation and a qualitative assessment.[11] The defending parties argue that the third step (exposure assessment) is not properly performed, because they contest the data used for the quantitative assessment (they contest the Klein assay, the bioavailability rate, the rate of endogenous production by pre-pubertal children, etc.), and they also argue that the qualitative assessment lacks scientific rigour (US). The defending parties may disagree,

[11] Inevitably, therefore, the fourth step was globally qualitative. See the 1999 SCVPH opinion, pages 69-73 and the replies to questions 1, 2 and 3, at pages 74-77.

but they cannot credibly argue that the European Communities has not completed the four steps of the risk assessment.

36. **For oestradiol-17β**, section 4.1.5, pare 36-39, of the 1999 Opinion is entitled "assessment of excess exposure to oestrogens from consumption of hormone-treated beef" and it explained why the JECFA ADI and the US acceptable levels are exceeded. This is a quantitative estimation and is meant to address the assumption of JECFA and of the US that oestradiol-17β acts only through receptor-mediated mechanism. It concluded that:

> [T]he FDAs acceptable daily intake (102 ng/person/day, see above) could exceed the daily production rate of oestradiol by 1,700 fold (of pre-pubertal children). While there is some experimental evidence in support of the currently used blood levels of oestradiol being 100 fold too high (Klein et al., 1994), the other assumptions used in coming to this conclusion may be too conservative. Thus, if absorption is reduced to 10% and the MCR for children is only 1/2 that of adults, the FDA acceptable daily intake could still be 85 fold too high.

37. In other words, the 1999 Opinion has made a quantitative estimate of the exposure assessment using the latest information and data available and also assumed 10% bioavailability, even if this low rate is scientifically questionable. Yet, even under such estimation, it concluded that the US acceptable daily intake "could still be 85 fold too high" (and, consequently, also JECFA's ADI of 0.50 ng/kg/bw/day would be exceeded). Accordingly, the European Communities fails to see why this is not the best possible quantitative estimate of the exposure assessment, taking into account the latest scientific information.

38. But the 1999 Opinion then goes on and contains sections 4.1.6 to 4.1.8, pages 39-43, which analysed the other mechanism by which oestradiol-17β is believed to act, i.e. by direct genotoxicity. An exposure assessment is again performed, but this time of a qualitative nature, where it states that: "[T]hese DNA-damaging effects indicate that no threshold exists for the risk from oestrogen metabolites" (at page 41). It also states that: "No data are currently available on the effects of exogenous low-dose oestrogens. However, genotoxic effects independent from the presence of hormonal receptors have been recognised for metabolites of certain oestrogens, as indicated above." (at page 42). It also states on the same page that: " These results indicate that induction of mammary tumors relies on the presence of E_2, but not that of the major oestrogen receptor, suggesting a genotoxic role of E_2 in the induction of these mammary tumors." It also arrived at a qualitative conclusion as follows:

> *In conclusion*, whereas it is clear that exogenous oestrogens, present in oral contraceptives or used in hormonal replacement therapy in women, are responsible for an increased risk of endometrial cancer and to lesser extent some increased risk of breast cancer, there is no direct evidence on the consequences of the contribution of exogenous 17β-oestradiol originating from the consumption of treated meat. Yet we know from the data derived from human populations within the ranges of physiological values of hormones in blood, that high levels are associated with an increased risk of breast cancer. Also known are the carcinogenic effects of 17β-oestradiol in experimental animals as well as the deleterious effects in pre- and perinatal development (see section 2). Finally, in consideration of the recent data on the formation of genotoxic metabolites of oestradiol, suggesting that 17ß-oestradiol acts as complete carcinogen, by exerting tumour initiating and promoting effects, it has to be concluded, that no quantitative estimate of the risk related to residues in meat could be presented.

39. **Ad (b).** The European Communities performed for the other **five hormones** the same risk assessment as that for oestradiol-17β. Indeed, a careful look at the 1999 SCVPH Opinion, confirms that all four steps were completed in the same way as for oestradiol-17β. Whilst completing the four steps, the SCVPH Opinions of 1999, 2000 and 2002, have taken care (unlike JECFA's assessments) to point to the numerous new scientific evidence, to the serious gaps in our knowledge and the scientific uncertainties surrounding many important aspects. It was the overall state of the file for each of these five hormones, and for each specific aspect required for the four steps of the risk assessment, which led the SCVPH to come to the overall conclusion that it was not possible to complete the risk assessment, in the sense of Article 5.1 *SPS Agreement*.

40. In addition, as for oestradiol-17β, the SCVPH performed an assessment of exposure assessment under realistic conditions of use of these hormones, taking into account misuse and potential abuse.

41. On the basis of these opinions the competent risk manager decided to apply Article 5.7 of the *SPS Agreement*. In particular, recital no 7 of the preamble to the Directive 2003/74 explains that: " As regards the other five hormones (testosterone, progesterone, trenbolone acetate, zeranol and melengstrol acetate), the SCVPH assessment is that, in spite of the individual toxicological and epidemiological data available, which where taken into account, the current state of knowledge does not make it possible to give a quantitative estimate of the risk to consumers". In other words, the European Communities based its measure on all the available pertinent information for each of the four steps of the risk assessment which it had performed.

Q9. Can the European Communities explain the meaning it gives to the term "mere doubt" in para. 181 of the EC second submission (US case)?

42. The use of the terms "mere doubt" (in para. 181 of the EC Rebuttal Submission) is made there in order to distinguish a situation where the available relevant evidence is sufficient from the situation where the pertinent evidence is insufficient. The term "mere doubt" does not mean any kind of doubt but doubt that is scientifically established, in other words in both cases the "sufficiency" or "insufficiency" of the relevant evidence should be scientifically established. Indeed, mere doubt could be found to be sufficient to take a measure in cases of substances or risks that are new or have not been evaluated before. For example, when in 1996 the European Communities took drastic measures against BSE the available relevant scientific evidence was very-very meagre and the prohibition was based essentially on doubts and possible associations.

43. Conversely, in situations where the substances have been evaluated before, the doubt should be serious, as the last sentence of para. 181 states. Typically, reasonably serious doubts may exist when the pertinent available evidence is contradictory, inconclusive or incomplete. This is related not only to the quantity of the available evidence, but frequently to the quality of the pertinent evidence. Serious doubts may appear or develop for the first time about the safety of a substance which is already authorised on the basis of developments in scientific research. The difficulty for the risk assessment and risk management is to decide when the pertinent evidence moves from a situation of being previously thought to be "sufficient" into a situation that is now found to be "insufficient" for the purposes of assessing risk in a way that does not compromise the chosen level of protection. The formal requirement of having to conduct a risk assessment is not a problem, because a risk assessment (with all four steps in a quantitative or qualitative manner) is nearly always possible to perform. The problem is when the new evidence points to credible scientific uncertainties, incompleteness of the data or contradictory findings. That is why all legal systems that aim to protect effectively human, animal or plant life and health provide that, in such situations, qualitative assessment is acceptable for some of the four steps in the risk assessment. As Article 5.7 of the *SPS Agreement* states, members may adopt measures "on the basis of available pertinent information" and should seek to obtain the additional information necessary "for a more objective assessment of the risk".

44. The European Communities has given the example of Carbadox (at paras. 150-152), where JECFA waited for a period of about 10 years in order to move from a situation of sufficient evidence to authorise Carbadox (in 1991) to a situation of sufficient evidence to prohibit Carbadox (2003). The question is who is to bear the responsibility for the adverse effects on human health during the period of ten years that lapsed in between? An interpretation of Article 5.7 that does not allow taking into account credible scientific developments and scientific uncertainty that question previously held scientific views is not correct. This point is quite different from the point that science always develops. To guard against potential abuses, as explained above, the new evidence should not be arbitrary[12] but credible and should show that there is genuine scientific disagreement identified in a risk assessment. This kind of scientific uncertainty should be acceptable under Article 5.7 of the *SPS Agreement*, if the right of members to choose their appropriate level of protection is to be preserved. Indeed, Article 2.2 of the *SPS Agreement* requires a measure to be based on scientific principles and not maintained without sufficient scientific evidence. But Article 2.2 does not lay down such requirements for provisional measures, because it states "except as provided for in paragraph 7 of Article 5".

Q10. The European Communities specifies that "it has issued a new call for scientific data and research from 2002 onwards, on substances with hormonal activity which may be used for growth promotion purposes in bovine meat". Could the European Communities specify what information it has actually requested? When does it expect to receive it?

45. The European Communities has referred to this call for scientific data in Para. 264 of its Replies to the Panel's Questions after the first substantive hearing and in Para. 169 of its Second Written Submission. A link to the OJ publication on the internet has been provided each time. For ease of reference the European Communities attaches the public call now as Exhibit EC-128. As can be seen from the document, the information requested was

> any scientific evidence (from 2002 onwards) on substances with hormonal activity which may be used legally in Third Countries for growth promotion purposes in bovine meat having oestrogenic, androgenic or gestagenic action since the *Last Review of the Assessment of Risks to Human Health from Hormone Residues in Bovine Meat and Meat Products* of the SCVPH in 2002 following the criteria outlined under item 3.

46. Under item 3 cited above it is specified, *inter alia*, that:

> EFSA encourages the submission of peer-reviewed data/publications (not just the reference) as the most relevant and reliable documents.

47. Five papers have been submitted following the call. EFSA is currently reviewing these five papers together with the final version of the UK Group report (see below Question 14) as it has been published in July 2006. An assessment is expected for April 2007.

Q11. What is meant by no "additive risk"? Please explain to which "risks" these are "additive".

[12] It should be noted that the Appellate Body had found in its 1997 *Hormones* report (at paras. 244-245) that the old EC Directive was not imposed for arbitrary or discriminatory protectionist reasons, contrary to the arguments of the defending parties at that time and the findings of the 1997 hormones panel. Moreover, none of the parties has argued in the present proceedings that the new EC measure is is based on arbitrary or discriminatory evidence. All of the Panel's experts have confirmed that the different views held by the defending parties and JECFA, on the one hand, and the EC, on the other, are based on legitimate and genuine scientific disagreement.

48. It is scientifically not disputed (in this case even by the defending parties) that life-time exposure of humans to the levels of endogenous production of oestrogen (and in particular to oestradiol-17β and its metabolites) and, most likely, to the other two natural hormones (testosterone and progesterone) are sufficient to cause and/or promote cancer in some individuals. This is frequently called risk of cancer from background (endogenous) exposure. This kind of exposure (and the attentive risk of cancer) **cannot be avoided**.

49. But humans are exposed daily to variable levels of residues of these hormones, in particular estrogen (including oestradiol-17β and its metabolites), from many exogenous sources where these hormones naturally occur, such as milk, eggs, broccoli, soya beans, etc. In scientific literature it is seriously disputed whether the estrogenic activity of residues in plants is the same, both as regards the mode of action and potency, when consumed by humans.[13] It is nevertheless not disputed that human exposure to such residues adds some more burden to the background levels. It is thus expected that this addition may increase the risk of cancer. It is important to note, however, that this kind of human exposure to levels of residues occurring in natural foods (exogenous exposure) **cannot be avoided**, unless the consumption of such natural foods is reduced or prohibited. But as the Appellate Body has explained in its 1998 *Hormones* report (at para. 221), this kind of prohibition is not possible as it would require such a comprehensive and massive governmental intervention in nature and in the ordinary lives of people as to reduce the comparison itself "to an absurdity". Indeed, it would require changing human diet and habits that have been practiced for centuries by human beings.

50. The concept of "additive" risk refers to exposure which is further added on humans from the levels of residues in meat from animals treated with these hormones for growth promotion. The risk of cancer[14] from this kind of exposure to residues from hormone-treated meat is "added" to the cancer risk from the existing (endogenous) exposure through the background levels of hormones and through the exposure to (exogenous) sources as contained in non-treated natural food. It is not disputed (see, e.g., the 2002 US Report on Carcinogenesis) that "veterinary use of steroidal estrogens to promote growth and treat illness can increase estrogens in tissues of food-producing animals to above their normal levels", in general substantially higher than the normal (endogenously produced) levels.[15] Therefore, it should be stressed that, unlike for the other two sources of exposure, exposure to residues from hormone-treated meat **is avoidable** because these hormones are chemical substances that are deliberately added in meat. See also the reply to Question 13 below for the regulatory implications from these different sources of exposure.

51. The risk of cancer from the consumption of residues in hormone-treated meat are "additive" (to risk of cancer from the two other sources of exposure), irrespective of whether these hormones are genotoxic carcinogens or only promote cancer through receptor-mediated mechanisms. Indeed, if they cause cancer by direct genotoxic action, the addition of such exposure increases the likelihood of the adverse effect to occur. If they act only through receptor-mediated mechanism, the risk from such

[13] See, e.g., Exhibit EC-35, which is a pioneering study in this area, of which neither the defending members nor JECFA were aware when they evaluated these hormones.

[14] For reasons of convenience, only the potential risk of cancer is mentioned here, although the 1999 opinion of the SCVPH has identified a number of other possible adverse effects on humans from exposure to exogenous hormonal residues, in particular from hormone-treated meat.

[15] The 1999 SCVPH contains data on the higher residue level in treated animals with these hormones (as compared to untreated animals). See tables 2 (for oestradiol-17β), 5 (for testosterone) and 7 (for progesterone). Since the other three synthetic hormones are not produced endogenously, their residues will always be additional. The 1999 SCVPH opinion is based on recent studies: see, e.g., Exhibit EC-11 (concerning melengestrol acetate showing that the US tolerance levels will be exceeded after administration of 1.5 mg/day, that is according to the recommended dosage of use in the US). See also Exhibits EC-14, 16, 17, 18, 47, 50, 53 and 78, which provide the most recent measurements of residues in meat from animals treated with these hormones for animal growth promotion according to GVP and in situations of abuse.

exposure will be again "additive", when they cause the presumed threshold to be exceeded. The risk assessment of the European Communities has established that oestradiol-17β is a proven genotoxic carcinogen and that the other two natural hormones (testosterone and progesterone) are also suspected to be genotoxic. Moreover, the risk assessment of the European Communities has also demonstrated that the ADIs recommended by JECFA for all these hormones will be exceeded under realistic conditions of use of these hormones in the US and Canada. They will also be exceeded in any case if the more recent data on the endogenous production of the natural hormones by pre-pubertal children is taken into account.

Q12. A 1999 Report of the Committee for Veterinary Medicinal Products of the European Communities refers to the low bioavailability of oestradiol 17β. How is this finding reconciled with references to bioavailability in the SCVPH Opinion? (please refer to comments by the parties on the Panel's Question 43 to experts)

52. The 1999 report of the Committee for Veterinary Medicinal Products (CVMP) (see Exhibit CDA-5) states, as regards oestradiol-17*β*, the following: "the bioavailability of 17β-oestradiol esters after oral administration is low (3% as unchanged 17β-oestradiol), but might be higher if estron, an estrogenic active metabolite, is included" (at p. 2).

53. First, it should be noted that the 1999 CVMP report does not cite any specific new literature in support of this statement. Indeed, of the scientific literature cited on pages 14 – 17 of that report, there appears to be no paper or study specifically relating to measuring bioavailability of oestradiol-17β. Consequently, the CVMP opinion must be simply reproducing on this point the JECFA evaluations of 1988 and 1999 for oestradiol-17β, and is not based on new scientific evidence.

54. Secondly, it is important to note that the last sentence from the above quoted 1999 CVMP report states that: "… but might be higher if estron, an estrogenic active metabolite, is included". Indeed, the JECFA reports and, by extension the 1999 CVMP opinion, have considered only some of the residues of oestradiol-17β in meat; in particular, they have not considered the lipoidal (fatty acid) esters nor estrone residues. This is important because lipoidal esters "represent about 40% of the total oestradiol-17β esters in fat meat shown in the metabolic study", and they are "about tenfold more active on uterotrophic assay than oestradiol-17β when given orally" (see Exhibit EC-51A, page 18). The two scientific studies by the European Communities (Exhibit EC-51A, and Exhibit EC-51C, at page 32) concluded that the residues of lipoidal esters and of oestrone have not been considered so far by any risk assessment known at the time (either by the defending members or the 1988 and 1999 JECFA assessments) and that it is imperative that they are taken into account in the calculation of bioavailability and the pharmacokinetics (see also Exhibits EC-9 and EC-117, both confirming these findings). It follows that the 1999 CVMP report, which is based on the old JECFA evaluations on bioavailability, can no longer be considered reliable. Conversely, the findings on bioavailability by the SCVPH in 1999 and 2002 are more accurate because they are based on more recent and pertinent scientific information.

55. Moreover, the European Communities has commented in detail on the comments made by the defending members on the Panel's Question 43 to experts and maintains entirely the comments it submitted on 12 July 2006 (at paragraphs 150-154). With its comments the European Communities has tried to explain why the data on bioavailability used by the defending parties and JECFA are most likely to be wrong for two reasons: 1) as just being explained above, because they do not take into account all the relevant residues in hormone-treated meat; and 2) because their estimate that bioavailability of oestradiol-17β is <10% is in itself not correct, for the reasons explained in the EC's comments of 12 July 2006 (at paras. 150-154).

56. Canada's comments of 12 July 2006 (at para. 93) do not help develop the debate further because Canada seems to espouse the argument of Dr. Boobis about the ADI representing a

"bioavailability adjusted" does. But even if the arguments of Dr. Boobis were correct (*quod non*), determining with accuracy the level of bioavailability is very important – instead of proceeding with mere assumptions as does JECFA – if we take into account the much lower endogenous production rates by pre-pubertal children in the calculation of the ADI and that multiple implanting of animals with these hormones is recommended by the manufacturers and currently practiced in the US and Canada.

57. The comments of the US of 12 July 2006 (at paras. 124-128, as well as at paras. 119-120 thereof) are confusing and misleading. The US comment (at para. 124) that "the *Lampit* study very clearly indicates that, to overcome the low bioavailability of estradiol 17β, very large amounts of the hormone must be administered orally to achieve a therapeutic effect" is wrong.

58. The *Lampit et al.* paper of 2002 (see Exhibit EC-99) states that: "The mini-dose of estrogen used here is based on an attempt to replace prepubertal estrogen levels. It is much lower than the low dose estrogen employed for growth acceleration in girls with Turner syndrome. Based on the relative estrogenic activity of conjugated estrogen and ethinyl E2 and a mean patient weight of 20 kg, it was calculated that the mini-dose is 12- to 28-fold weaker than the usual low dose of 100 ng/kg ethinyl E2 given for growth acceleration." (at page 689, footnotes omitted).[16] Contrary to what the US argues, therefore, the 2002 *Lampit et al.* paper states that very low doses suffice to observe biological action in pre-pubertal children, which must mean that bioavailability of oestradiol-17β at those very low doses cannot be insignificant.

59. More importantly, however, the US comments (in para. 124) that "very high doses are required to elicit the desired therapeutic effect" is misleading because such high doses are not administered (at least not only) in order to elicit the desired therapeutic effect but in order to elicit it **quickly**, otherwise the treatment will not be therapeutic. Therefore, from the high doses used for therapeutic treatment, it does not follow (as the US argues) that such doses are necessary because of the low bioavailability of oestradiol-17β.

60. Finally, the other US comments of 12 July 2006 (at paragraphs 125-128) do not help us develop the debate further, as the US misinterprets the EC arguments and the opinion of Dr. Guttenplan. Moreover, the US comment in para. 128 is confusing, because all the scientists confirmed that the bioavailability of the three synthetic hormones (trenbolone acetate, zeranol and melengestrol acetate) is not known. Whether JECFA assumed 100% bioavailability for these synthetic hormones is another issue, as explained above, and this is not the point the EC was making when arguing that the bioavailability of the three natural hormones by the defending parties and in the JECFA evaluations has been underestimated.

Q13. In its comments on replies of experts to Panel Question 19 (para.75) Canada asserts that a recent Opinion of the European Food Safety Agency (EFSA) recognizes thresholds for genotoxic substances. Please elaborate.

61. The European Communities fails to understand why Canada made the reference to the opinion of EFSA of 18 October 2005 (see also exhibit CDA-46), because that document does not support Canada's claim.

62. It should first be noted that Canada does not quote in its entirety the paragraph in question from the EFSA's opinion (cited at para. 75 of Canada's submission). The paragraph in question reads as follows:

[16] Incidentally, the 2002 Lampit et al. paper cites with approval the calculations of endogenous production rates of pre-pubertal children estimated by the Klein et al. assay, which the Lampit paper explicitly characterises "as the landmark report by Klein et al." (at p. 689).

> The Scientific Committee concludes that based on the current understanding of cancer biology there are levels of exposure to substances which are both genotoxic and carcinogenic below which cancer incidence is not increased (biological thresholds in dose-response), **however, numerical values for such levels of exposure cannot be identified on scientific grounds at the present time.** (the highlighted phrase was left out by Canada).

63. More importantly, however, the opinion of EFSA has clarified very clearly that the purpose for which it was provided is different from the one mentioned by Canada. The EFSA opinion states that the margin of exposure approach is for "cases where substances that are both genotoxic and carcinogenic have been found in food, irrespective of their origin, and where there is a need for guidance on the possible risks to those who are, or have been, exposed" (at page 21). This means that this approach applies only for substances that **occur or develop naturally** in food or the environment (e.g. the aflatoxins in dried food or the naturally occurring oestrogens in broccoli or in eggs, etc.).[17] This is explained at page 5 of EFSA's Opinion which states:

> Undesirable substances occur in food (for example as an inherent natural constituent in the food plant or as contaminant through their presence in the environment, through fungal contamination or through preparation processes). The general need to minimise exposure to such substances, when they are demonstrated to present a carcinogenic and genotoxic hazard, is expressed in the ALARA (as low as reasonably achievable) principle. The opinion of the Scientific Committee addresses approaches beyond the ALARA principle allowing a level of potency assessment of specific substances which are present in food and which are both genotoxic and carcinogenic. Such an approach will not substitute for minimising exposure to all such substances. It will ensure that, where resources are limited, the highest priority is given first to those substances which present the greatest risk for humans.[18]

64. But acceptable margins of exposure do not apply for chemical substances (like the six growth hormones) which are intended to be **deliberately** added (i.e. administered exogenously) to food. Authorisations for such chemical substances to be added deliberately to food, feed or the environment are not granted. Canada has apparently not read the other relevant parts of EFSA's Opinion which explain this as follows:

> The Scientific Committee is of the opinion that in principle substances which are both genotoxic and carcinogenic should not be deliberately added to foods or used earlier in the food chain if they leave residues which are both genotoxic and carcinogenic in food. (at pages 5 and 21).

65. The reason for which the EFSA opinion came to this conclusion is that:

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[17] See, e.g., Commission Regulation (EC) No 1525/98 (O.J. L 201, 17.7.98, p. 43) which has sought to eliminate or reduce exposure from aflatoxins in dried food or in milk on the following grounds: "Whereas aflatoxins, in particular aflatoxin B1, are genotoxic carcinogenic substances; whereas for substances of this type there is no threshold below which no harmful effect is observed; whereas no admissible daily intake can therefore be set; whereas current scientific and technical knowledge and improvements in production and storage techniques do not prevent the development of these moulds and consequently do not enable the presence of the aflatoxins in food to be eliminated entirely; whereas it is, therefore, advisable to set limits as low as possible" (see 5th recital of the preamble).

[18] Indeed, the EC has a consistent record of taking the measures necessary to reduce or eliminate risks from the naturally occurring genotoxic and carcinogenic agents. See, e.g., Council Regulation (EEC) 315/93 laying down Community procedures for contaminants in food (O.J. L 37, 13.2.1993, p.1), which has been amended several times and most recently by Commission Regulation (EC) 466/2001, O.J. L 77, 16.3.2001, p. 1.

> For genotoxic substances which interact with DNA, directly or after metabolic transformation (direct-acting genotoxic chemicals), the absence of a threshold in their mechanism of action is generally assumed, i.e. there is no dose without a potential effect. (at page 5)

66. The European Communities takes this opportunity to stress that it has a consistent and coherent record of prohibiting chemical substances that are both genotoxic and carcinogenic when applications for authorisation in order to be deliberately added to food, feed or the environment are made. It has prohibited a number of chemical substances once experiments on animals have shown that they are genotoxic carcinogens or they were suspected of having such properties, for instance:

- the withdrawal of the authorisations for Carbadox and Olaquindox in 1998,[19] well before JECFA and Canada did so;
- the withdrawal of the authorisation for the coccidiostat Nifursol in 2002;[20]
- the withdrawal of the authorisation for a number of flavouring substances, such as methyleugenol and estragol in 2002;[21] propyl 4-hydroxybenzoate and pentane-2,4-dione in 2005;[22] and acetamide in 2006.[23]

67. The European Communities would like to address another related error in the reply of Dr. Boobis to written question No 11 of the Panel, where he made reference to the pesticide daminozide (a suspected genotoxic carcinogen) and implied that "there may be kinetic or dynamic factors indicating that although theoretically there was no exposure with zero risk, in practice the risk would be minimal and therefore acceptable". The statement by Dr. Boobis is misleading, however, because the administration of daminozide has not been approved for edible crops but only for **non-edible** plants (flowers), something he does not explain.[24]

68. In conclusion, therefore, a distinction should be made between genotoxic carcinogens that are occurring or developing naturally in food (e.g. nitrate, aflatoxins, broccoli, soyabeans, and eggs) and the chemical substances that are intended to be added deliberately to food (e.g. carbadox, the six hormones for animal growth promotion, etc). For the former, there is not much that can be done other than take measures to reduce or eliminate the risk to the extent possible. For the latter, however, refusal to authorise their use is an effective means of preventing their addition to food, so as to achieve the chosen level of protection. The European Communities hopes this will clarify that there is no basis in the confusing argument of the defending parties that, since human beings are exposed to estrogens from so many sources (endogenous animal and human production and exogenous intake from natural foods), the small addition from the residues in hormone-treated meat would pose no risk. The European Communities contests the simplistic logic of this unscientific argument by the defending parties that, unfortunately, has found its way also in the evaluations of JECFA.

69. The European Communities can therefore confirm that it applies consistently a policy on risk analysis that prohibits the authorisation of chemical substances which are suspected or proven to be genotoxic carcinogens when they are intended to be added deliberately to food. This is in order to achieve its level of health protection of no (avoidable) risk, that is a level of protection that does not

[19] See Commission Regulation (EC) No 2788/98, OJ No L 347, 23.12.1998, p. 31-32.
[20] See Council Regulation (EC) No 1756/2002, OJ No L 265, 3.10.2002, p. 1.
[21] Commission Decision 2002/113/EC of 23.1.2002, OJ No L 49, 20.2.2002, p.1.
[22] Commission Decision 2005/389/EC of 18.5.2005, OJ No L 128, 21.5.2005, p. 73.
[23] Commission Decision 2006/252/EC of 27.5.2006, OJ No L 91, 29.3.2006, p. 48.
[24] See Commission Directive 2005/53/EC of 16.9.05, OJ No L 241, 17.9.2005, p. 51, at page 55, point 105.

allow any unnecessary addition from exposure to genotoxic chemical substances that are intended to be added deliberately to food. The risk from residues in hormone-treated meat is such an avoidable risk, and this is what the European Communities aimed to achieve when it adopted the Directive 2003/74/EC.

Q14. Has the draft assessment of the UK Group (referred to in para.187 of the European Communities' rebuttal submission) already been assessed by EFSA or other relevant institutions? If so, what are the conclusions?

70. As mentioned in its reply to Question 12 above, the UK Group adopted the final version of its report in June 2006.[25] EFSA is currently reviewing this report. An assessment is expected for April 2007.

71. A mere reading of the report's conclusions and recommendations, however, already shows that the UK Group has considerably changed its assessment since the last assessment it had carried out in 1999 (to which the SCVPH reacted with its 2000 Opinion). Indeed, while the 1999 UK assessment maked a number of bold "no evidence" conclusions, for example on mutagenic/genotoxic activity or threshold considerations, the 2006 UK report contains conclusions which are very nuanced and put heavy emphasis on the fact that the scientific data are incomplete and that many uncertainties remain and need to be studied. The European Communities recalls that when Directive 2003/74/EC was adopted by the European Parliament and Council, the United Kingdom did not vote against the Directive.

72. Thus, on mutagenic/genotoxic activity, the report now refers to the "weight of available evidence [which] suggests that likely levels of human exposure to hormonally-active substances in meat from treated animals would not be sufficient to induce any measurable biological effect" and goes on to state that "specifically, it is very unlikely that the presence of 17β-oestradiol and its metabolites in meat from treated animals would significantly increase the risk of adverse effects in consumers." That conclusion is based on a number of important "qualifications and reservations" including the assumption that there is a "correct" or "recommended" use of the exogenous hormonal substances and the reservation that all scientific data relate to single substances only and not to their combined use.

73. Absence of information and scientific uncertainty is also the reason why not all of the conclusions were supported by all members of the UK Group (note that the press release speaks of two dissenting opinions). Indeed, the following is stated under "qualifications and reservations":

> the Working Group had to decide what to do in the absence of information or where there was uncertainty of interpretation of information. One Member expressed the view that for the substances under consideration, there was a large element of uncertainty, so the precautionary principle should become the primary consideration. The many uncertainties associated with the current lack of knowledge could be addressed by further research where this was both feasible and affordable. The Working Group was unanimous that all uncertainties must be made clear, especially those that were considered crucial in the risk assessment process.

74. The report states clearly that "there are important gaps in the evidence base that preclude producing definitive risk assessments for 17β-oestradiol or the other five hormonally-active substances". (at point 6 of the executive summary). It is significant to note that the report further states (at point 6) that:

[25] Press release of 5 July 2006 and report available at http://www.vpc.gov.uk/.

> Not all data gaps are equally important for the purposes of risk assessment and the Working Group highlighted a number that could improve future risk assessments. As an example, it would be helpful if the CVMP and JECFA could make available data on pharmacokinetics and metabolism of assessed compounds that were supplied in manufacturers' dossiers. This openness and transparency would allow greater public scrutiny of the facts and confidence in the hazard and risk assessments produced.

75. Indeed, this is what the European Communities has been arguing, namely that the CVMP and the JECFA evaluation would have to be opened to transparent procedures and provide the old evidence on which their assessments were based in order to enable an objective and transparent re-evaluation of these substances. Moreover, the UK report's conclusions end with a list of things that "need to be established in order to improve future risk assessments." It is worth quoting some of the important gaps that are listed in points 7 to 9 of the executive summary, as it takes up many of the points on which the European Communities has argued that there is scientific uncertainty:

- the precise relationship between the potential use of growth-promoters and concentrations of residues in meat
- levels of exposure in consumers
- dose-response relationships for the effect of hormonally active substances (and their metabolites) in experimental animals and humans
- the bioavailability, metabolism and possible bioaccumulation of lipoidal esters of oestrogen following ingestion of meat from implanted cattle
- the possible synergistic effects of cocktails of hormonal substances
- a validated technique to detect and assign low residual concentrations of oestradiol in the finished edible products to natural sources or implant residues.

Q15. What steps has the European Communities taken to request re-evaluation of the existing international standards for the five hormones, <u>according to the procedures of JECFA or Codex</u>? Please provide documentation.

76. First, it is worth recapitulating what the European Communities did (as described at para. 96 *et seq.* (WT/DS320), paras. 79 *et seq.* (WT/DS321) of its Second Written Submission). The European Communities informed Codex and the JECFA Secretariat in May 1998 that it was carrying out new risk assessments on the six hormonal substances in question and that it had launched a series of specific studies.[26]

77. Upon learning that JECFA, on its own initiative, has decided to re-evaluate the three natural hormones, the European Communities, by letter of 31 July 1998 to Codex and letter of 27 November 1998 to JECFA requested that this re-evaluation be postponed until the results of the studies commissioned have come in.[27] An indicative list of the 17 studies was attached to the letter. However, both Codex and JECFA declined to heed to this request, without any valid reason.[28] At the 11th

[26] See reference to letter of 7 May 1998 in EC-Exhibit 63 – No 13: letter to Mr. Orriss, Chief of Joint FAO/WHO Food Standard Programme, dated 31 July 1998.

[27] See EC Exhibit 63 – No 13 and No 14 (letter of reply to letter sent on 27 November).

[28] See EC Exhibit 63 – No 14 (letter from Mr. Herman, JECFA Secretariat, dated 23 December 1998)

session of the CCRVDF in late June 1999, the European Communities re-iterated its request, to no avail.[29]

78. Second, according to JECFA's procedural rules there are five ways of placing veterinary drugs on the agenda for (re-)evaluation.[30] These are the following[31]:

> **1. Codex committees**
>
> The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) refers substances to JECFA based on priorities that it establishes using criteria that it has developed that are in accord with accepted procedures of the Codex Alimentarius Commission.
>
> **2. FAO and WHO Member States**
>
> FAO and WHO Member States may request the inclusion of veterinary drugs on the agenda of JECFA through a direct request to the FAO and WHO Secretariats. Such a request must be accompanied by a commitment to provide the necessary data 6-7 months before the meeting.
>
> **3. Sponsors**
>
> For veterinary drugs not previously evaluated by JECFA, an industry sponsor may forward a request for evaluation through the government of a Member State to CCRVDF, with a commitment to provide the relevant data. Requests for the re-evaluation of a veterinary drug that has been reviewed by JECFA previously may be forwarded directly to the JECFA Secretariat. As with all other substances on the agenda, the Joint Secretariat includes the substance in the call for data for the meeting to ensure that all interested parties have the opportunity to submit data.
>
> **4. JECFA Secretariat**
>
> The JECFA secretariat may place a veterinary drug on the agenda for re-evaluation even though no outside request has been received.
>
> **5. JECFA itself**
>
> The Committee often establishes a temporary ADI or recommends temporary MRLs, with a request for further data by a certain time. These veterinary drugs, which have the highest priority for evaluation, are placed on the agenda of the appropriate meeting by the Joint Secretariat.

79. The first listed here is the "priority list" procedure described by Dr. Myagishima at the expert meeting. The European Communities has, since the events described above, not made a formal

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[29] See para. 125 of the Report of the Eleventh Session of the Codex Committee on Residues of Veterinary Drugs in Foods (ALINORM 99/31), available at http://www.codexalimentarius.net/web/archives.jsp?year=99.

[30] Note that two sets of procedural guidelines govern JECFA's work, one issued by the WHO and one issued by the FAO. The former is available at http://www.who.int/ipcs/food/jecfa/procedural_guidelines%20_drugs.pdf, the latter at ftp://ftp.fao.org/es/esn/jecfa/2002-09-24_Vet_Drugs_Proc_Guidelinesb.pdf.

[31] In respect of the five ways of having a substance (re-)evaluated, the two abovementioned sets of guidelines are identical. The text reproduced above is the Annex 1 of the respective guidelines.

request to have any of the six hormonal substances in question put on the priority list. As explained at the hearing, however, the European Communities may do so once the new risk analysis principles on residues in veterinary drugs have been adopted.[32]

80. Note, however, that this first way, contrary perhaps to what may have transpired at the expert meeting, is not the only possibility for a Member to request evaluation of a substance through JECFA. Indeed, as can be seen from the above point 2, there is also the possibility for a Member to directly request such evaluation from either FAO or WHO. What the European Communities has done as described above can be subsumed under this second way of requesting (re-)evaluation of substances. As seen above, the European Communities turned directly to FAO (the EC was only a member of FAO – not Codex Alimentarius – at that time) to inform it of the new ongoing risk assessments on all six substances and to request the postponement of the impending re-evaluation of the three natural hormones until after the results of the 17 studies would be available. Obviously, this implies a commitment to make the results of these risk assessments and 17 studies available to JECFA. Equally obviously, this avenue became obsolete with JECFA's refusal to postpone for a period of 2-3 years the re-evaluation of the three natural hormones.

81. Note, furthermore, that under the above rules (point 4), the JECFA Secretariat can also decide on the (re-) evaluation of a substance on its own initiative. This is what the JECFA Secretariat has indeed done with regard to the three natural hormones. Note finally, that when performing an evaluation, the temporary advisor (i.e. a member of the JECFA secretariat put in charge of preparing working papers on the substance in question on the basis of available data) is asked to perform a literature search on the substance in question.[33] In light of these facts, it is clear that JECFA has had every opportunity, after the European Communities' repeated raising of the issue of the new risk assessments, to postpone the 1999 risk assessment and to place again these hormones for evaluation after 2002.

82. Moreover, the Delegation of the European Community referring to its written comments contained in CX/RVDF 06/16/7, Add.1, stated that the MGA was evaluated by JECFA as growth promoters and that such use of hormones with estrogenic, androgenic or gestagenic action was prohibited in the European Union. The prohibition was permanent for Oestradiol 17beta and provisional for the other hormonal substances. The 2002 review of the Scientific Committee on Veterinary Measures (SCVHP) relating to Public Health considered the report on MGA prepared by the 54th meeting of JECFA and observed that it provides a comprehensive review of the pharmacokinetic/toxicokinetic parameters and toxicological properties of MGA in various species. The Delegation argued, however, that no original data were presented in the review and the majority of references were reports that had not been published in the peer-reviewed scientific literature. Therefore, for MGA, concerns remained that excess intake of hormone residues and their metabolites, endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects could be envisaged, in particular for susceptible risk groups. For these reasons, the European Communities could not support the adoption of the MRLs proposed by the 66th JECFA. This position was supported by two other delegations.

[32] Proposed Draft Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Food (for inclusion in the Codex Procedural Manual), Appendix VIII of ALINORM 06/29/31 (report of 16th CCRVDF) Available at http://www.codexalimentarius.net/web/archives.jsp?lang=en]. As explained at the hearing, the new Paragraphs 19 and following of these principles provide the CCRVDF as the risk manager with much more concrete possibilities to give specific instructions to JECFA on which aspects to cover in its risk assessment. Given that the EC risk assessments on the six substances in question raise many issues which have so far not been addressed by JECFA, it is obvious that the European Communities would want JECFA to be instructed to specifically address these issues.

[33] Both the WHO and the FAO guidelines underline the importance of this literature search, see WHO guidelines, page 6 in bold, see FAO guidelines, point 5.2.

83. The following were the EC written comments on the matter delivered in time before the meeting and submitted to everybody in CX/RVDF 06/16/7, Add.1:

> **Melengestrol acetate:** The substance was evaluated by JECFA for use as growth promoters. Such use of hormones with estrogenic, androgenic or gestagenic action is prohibited in the European Union. This provision is permanent for oestradiol 17B and provisional for the other hormonal substances. It is also in line with Article 5.7 of the SPS Agreement. It applies while the Community seeks more complete scientific information. The European Commission (by means of the Scientific Committee on Veterinary Measures relating to Public Health – SCVPH, and now the European Food Safety Authority – EFSA) reviews regularly any additional scientific data from all possible sources that is publicly available. This entails continuing to review, as done in 2000 and 2002, the availability of scientific publications and evaluation reports.
>
> The 2002 review of the Scientific Committee on Veterinary Measures relating to Public Health considered the report on melengestrol acetate prepared by the 54th meeting of JECFA and observed that it provides a comprehensive review of the pharmacokinetic/toxicokinetic parameters (adsorption, distribution, metabolism and excretion) and toxicological properties of MGA in various species. It criticised, however, that no original data are presented in this review and the majority of the references are to reports that have not been published in the peer-reviewed scientific literature. The 54th JECFA report itself states that "*Most of the studies were conducted before 1979 according to the standards in existence at that time and were not carried out in compliance with GLP*" (page 65, 3rd paragraph of 54th JECFA Report) and the 62nd JECFA presented only new information regarding the structure and activity of the metabolites of MGA (page 22 of 62nd JECFA Report).
>
> The EU scientific committee considered more recent investigations and summarised (see page 17 to of the SCVPH report of 2002[2]). Preliminary data cited in this report:
>
> – indicated that the metabolism of MGA is more complex that previously assumed, but further experiments should verify the specific metabolite pattern in target animal species as well as man;
>
> – demonstrated that MGA has a very strong potential to bind to bovine progesterone receptors, although these data need further verification;
>
> – suggested that *in utero* or pre- and peripubertal exposure to hormones (including animal evidence on synthetic products) may affect pubertal development and epidemiological studies with opposite sexed twins indicate that prenatal exposure to hormones may be linked to adult cancer risk;
>
> – showed that newer experiments clearly identify a risk for excessive exposure of consumers to residues from misplaced or off-label used implants and incorrect dose regimes. In these cases, levels of oestradiol and its metabolites in muscle, fat, liver and kidney from hormone treated cattle may be 2-fold up to several hundred folds higher as compared to untreated meat. The level of increase depends on the treatment regime and the actual hormone levels in the implants used.
>
> Therefore for melengestrol acetate concerns remain that by excess intake of hormone residues and their metabolites, endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects could be

envisaged, in particular for susceptible risk groups persist. The European Community can therefore not support the adoption of the proposal for maximum residue limits for this substance. The next revision of its scientific opinion by EFSA is to be presented later in 2006. There has been a respective call for data at: http://www.efsa.eu.int/index_de.html. The European Community suggests that this substance is sent back to JECFA for re-evaluation in the light of the latest information provided in the 2002 and the expected 2006 risk assessments by the scientific committees of the European Community.

Q16. Please explain the reason for the differences between the "list of the 17 studies" that was appended to the 2002 Opinion and the one that was provided to the Panel. (please see paragraph 20 of the United States' Rebuttal Submission and its Table 1)

84. As explained above under Question 3, when the 2002 Opinion was issued all except two of the studies had already been published. Differences in the two lists are mainly the result of further publications of partial aspects of the studies. The European Communities is annexing as Exhibit EC-129 a commented version (track changes) of the US Table 1 referred to in the above question. It sets out in detail where and when the different studies have been published.

ANNEX C-2

COMMENTS BY THE EUROPEAN COMMUNITIES ON THE REPLIES OF THE UNITED STATES AND CANADA TO QUESTIONS POSED BY THE PANEL AND OTHER PARTIES AFTER THE SECOND SUBSTANTIVE MEETING

(31 October 2006)

Panel Questions to all parties:

Q1. With reference to the statement by the European Communities, *inter alia* in para. 12 of the EC reply to Question 3 of the United States, do the parties consider that a Panel is entitled to address "systemic claims" or issues related to "systemic obligations" and, if so, to what extent?

1. There does not seem to be a disagreement among the parties as to the substance of this question: all agree that the Panel has the task of ruling on the claims that the European Communities has made under Article 23 of the DSU irrespective of whether one wants to call them "systemic" or not.

2. Obviously, the parties' views differ on the question of how far the obligations contained in Article 23 go. Canada reiterates its view that it is the EC and not Canada that is acting unilaterally by proclaiming compliance. In its response, Canada's also overlooks one of the central EC claims in this dispute, namely the breach of Article 23 that lies in the fact that the US and Canada failed to have recourse to the DSU to seek redress of a violation, and instead unilaterally determined that the EC continued to be in breach of WTO obligations. The US, while being polemic, does not bother to explain its view on the extent of these obligations. It merely dismisses the European Communities' reading as an attempt "to see the DSU redrafted, at least for purposes of this dispute."

3. Fact is, however, that this Panel has the task of applying Article 23 to the situation at hand: A Member, in good faith, presents its compliance measure and nevertheless has to suffer continued application of sanctions, because the other side denies that compliance has been achieved and refuses to initiate the dispute settlement proceedings foreseen in Article 21.5. It is the first time that this situation arises in the dispute settlement system. Is it a situation that the DSU does not address? Neither side in this dispute says so. The parties merely have differing views on how to interpret Article 23 and Articles 21.5 and 22.8 when applied to this situation.

4. For some of the parties involved in this dispute, these views, not surprisingly, are related to positions taken in the current DSU review, in Canada's case since rather recently (see EC's response to Panel question No. 64)[1]. Indeed, not surprisingly, the current DSU review, amongst other issues, addresses this one, in order to precisely solve – through negotiation – the existing divergence of views on how the DSU should be applied in this situation. This is a not uncommon phenomenon in the WTO system: The correct interpretation of obligations is subject to disagreement among members and there is an initiative to settle that disagreement through political consensus.[2] Such initiatives are not always crowned by success or – as the present case shows – do not reach a result in time to address a given situation when it arises. The obligations – disputed as their content may be – do, however, exist. Thus, in the absence of an explicit clarification of the existing obligations by the collective

[1] See paras. 205 et seq. of the EC Replies to Panel's Questions after First Substantive Hearing, erroneously called Question 60.

[2] Another example is the role of multilateral environmental agreements in the interpretation and application of the WTO agreements. "Zeroing" methodology may serve as a further example.

Membership itself, it is for the dispute settlement bodies to discharge their duty to apply and interpret the rules that exist today. Even if there were a prospect of a conclusion of the DSU negotiations in the very near future, there is in no event a *non liquet* option of saying "we will wait for the outcome of the negotiations."

Q2. With reference to the US rebuttal, para. 27, do the parties consider that a measure that does not comply with the requirements of Article 5.7 SPS would automatically be in breach of Article 2.2 SPS, or Article 5.1 SPS, or both?

5. There seems to be agreement among the parties on the point that there is no automatic breach of Articles 2.2 and 5.1, if a measure does not comply with the requirements of Article 5.7. Indeed, the legality of a measure based on Article 5.7 can be determined independently of the requirements of Articles 2.2. and 5.1, since Article 5.7 is an exception to both of them. This is because, in addition to the comments made at paras. 3-5 of the EC's replies of 18 October 2006, it is necessary to take into account the reasons for which, in a given situation, all the requirements of Article 5.7 SPS are found not to have been complied with. It should be noted that the basic obligation under Article 2.2 SPS is to base the measure on sufficient scientific evidence. The performance of a risk assessment, in the sense of Article 5.1-5.2, is one way of providing such proof. However, as the experts have argued in the case of prohibiting tobacco smoking, it was not necessary to perform a risk assessment in the sense of Article 5.1 before taking a measure in the light of the overall scientific evidence available.

6. The European Communities would, however, agree with the US and Canada that in the present cases the recommendations and rulings of the DSB had identified a breach of Article 5.1 which the EC compliance measure needs to address. But no such breach exists any longer, if either of the following two situations applies: the measure is now based on a risk assessment and therefore consistent with Article 5.1; or the measure is based on Article 5.7 because the relevant scientific evidence is not sufficient to carry out a full risk assessment in the sense of Article 5.1 SPS.[3] However, the European Communities disagrees with the US comment (at para. 5 of its reply of 18 October 2006) that "the EC does not claim to have performed a risk assessment consistent with Article 5.1". This is not true. The EC has performed such a risk assessment for oestradiol-17β. Moreover, the EC has performed such a risk assessment also for the other five hormones. In the performance of such a risk assessment, however, the EC has come to the conclusion that for the five hormones it was not possible to complete the risk assessment because the relevant scientific evidence was insufficient on a number of important issues and points that are clearly identified and explained in the risk assessment. That is why the EC had to base its measure for the five hormones on Article 5.7 SPS, until "the additional information necessary for a more **objective** assessment of risk" becomes available.

7. The basic error in the US's and Canada's reasoning stems from their narrow (black or white fashion) interpretation of the term "insufficient": by employing default presumptions, safety factors, and the weight of evidence approach, they eliminate any "insufficiency" that comes from incomplete or contradictory evidence or from divergent or minority scientific views. Their approach views as predominantly, if not exclusively, quantitative the concept of "insufficient" evidence. This is, however, contrary to the findings by the Appellate Body which has stated that:

> "Article 5.1 does not require that the risk assessment must necessarily embody only the view of a majority of the relevant scientific community. In some cases, the very existence of divergent views presented by qualified scientists who have investigated the particular issue at hand may indicate a state of scientific uncertainty. Sometimes the divergence may indicate a roughly equal balance of scientific opinion, which may itself be a form of scientific uncertainty. In most cases, responsible and

[3] As is already known from previous submissions the parties disagree on the nature of Article 5.7. This does in principle not affect the above statement.

> representative governments tend to base their legislative and administrative measures on "mainstream" scientific opinion. In other cases, equally responsible and representative governments may act in good faith on the basis of what, at a given time, may be a divergent opinion coming from qualified and respected sources. By itself, this does not necessarily signal the absence of a reasonable relationship between the SPS measure and the risk assessment, especially where the risk involved is life-threatening in character and is perceived to constitute a clear and imminent threat to public health and safety. Determination of the presence or absence of that relationship can only be done on a case-to-case basis, after account is taken of all considerations rationally bearing upon the issue of potential adverse health effects." (at para. 194 of its report in Hormones),

and that:

> "Thirdly, a panel charged with determining, for instance, whether "sufficient scientific evidence" exists to warrant the maintenance by a Member of a particular SPS measure may, of course, and should, bear in mind that responsible, representative governments commonly act from perspectives of prudence and precaution where risks of irreversible, e.g. life-terminating, damage to human health are concerned." (at para. 124 of its report in Hormones)

8. It follows from the above that a measure would be in conformity with Article 5.1 if acted in good faith and on the basis of what may be a divergent opinion coming from qualified and respected sources. As the Appellate Body has said, such a measure would not necessarily signal the absence of a reasonable relationship with the risk assessment, in the sense of Article 5.1. SPS. *A fortiori*, therefore, a good faith measure that is based not on the mainstream but on divergent scientific opinions would also be in conformity with article 5.7 SPS.

Q3. When and how was each of the following documents made available to Canada and the United States? Please answer independently for each of the documents mentioned below:

(i) 1999 Opinion;
(ii) 2000 Opinion;
(iii) 2002 Opinion;
(iv) each of the "17 studies".

9. The European Communities considers that it has, in its replies to Question 3 and 16 and on many instances previously, demonstrated in ample detail not only that all three Opinions and the 17 studies (except two of them) were publicly available, but also that there was a continuous discussion about them with the defending parties on the bilateral and on the multilateral level throughout these years. Any suggestion that a Member was left in the dark about the progress and the results of the new risk assessment or that it was not in the possession of the 17 studies is not only baseless but borders on bad faith.

10. The US further argues (at paras. 7-10 of its reply of 18 October 2006) that the EC had to request from the US for the 2000 and 2002 risk assessments "a discussion or a conference on the scientific underpinnings of the EC's ban", as it did for the 1999 risk assessment. But there is no provision in any of the WTO Agreements relevant to this dispute that would place such a burden on the EC.[4] Quite the opposite, the important point is whether the US could have had access to the relevant evidence underpinning the EC risk assessment, if it had so wished. Indeed, about this there is

[4] The fact that the scientists from both sides met in July 1999 and discussed the first risk assessment was because of the good will of the EC, not because of any particular obligation on the EC under the WTO Agreements applicable in this case.

no doubt since the 1999, 2000 and 2002 risk assessments and all the underlying evidence on which they are based were published in peer-reviewed journals and where thus accessible to the US. This contrasts sharply with the persistent refusal by the US and Canada (and also of JECFA) to make available the underlying scientific studies upon which they claim to have based their risk assessments.

11. The burden, therefore, was on the US to submit any observations and comments, if it had so wished. The US failed to react even after the draft and the finally adopted EC measure was formally notified to the WTO in accordance with the SPS Agreement.[5] The December 2004 request by the US is a belated attempt to camouflage its lack of due diligence and bad faith for the resolution of this dispute.

Q4. Has the European Communities assessed in a systematic manner the existence and level of risks from failure to observe good veterinary practices with respect to the administration of oestradiol 17β as a growth promoting hormone to cattle, in particular in the United States' and Canada's markets? If so, please indicate where this assessment is to be found in the evidence provided to the Panel.

12. The EC disagrees with the US comment that "the EC has not even seriously argued in the course of these proceedings that it has done so" (at para. 11 of its reply of 18 October 2006).

13. The US resorts again to its favourite tactic in arguing that the EC presented only "unrealistic misuse scenarios" and that the evidence is "purely speculative and unsupported", without engaging in any serious discussion about the evidence that is presented to the Panel. Thus, the US does not mention nor discuss the following:

14. In Exhibit EC-73 the following undisputed instances of misuse or abuse are clearly mentioned:

- At para. 15: "In 1986, the USDA's Food Safety and Inspection Service (FSIS) reported a widespread misuse of hormone implants in the USA."

- At para. 16: "European Commission inspection mission to Canada in 1998 reported that the official laboratory of the Canadian Food Inspection Agency (CFIA) in Saskatoon had recently detected increased residue levels of beta-trenbolone in neck muscles of veal calves, exceeding the "administrative action level" of 2 ppb in muscle. The reported levels of up to 12 µg/kg in muscle cannot be achieved by implanting in the ear only in accordance with GVP." (footnotes omitted)[6]

- At para. 17: "It should also be noted that neither the US nor the Canadian meat inspection regulations provide for regular checks of the carcasses for misplaced implants at slaughter. Neither the US nor Canadian authorities offer any other adequate information which would allow the European Community authorities to verify the magnitude and frequency of misplacement of implants." (footnotes omitted)

[5] The US argues (at para. 9 of its reply of 8 October 2006) that instead of evidence "the EC response contained internet links for the 2000 Review and the 2002 Opinion". The important point to note, however, is that the US has apparently never tried to access the internet links provided by the EC, because had it done so it would have had access to all the references and materials on which the EC based its risk assessments.

[6] The EC Mission reports resulting from inspections carried out in Canada and the US are provided in Exhibits EC-67 and 68.

- At para. 22: " Implanting strategies commonly applied in today's beef production include not only re-implanting as a rule, resulting in the presence of several implants per animal, but also a shortening of intervals between the last application of an implant and the slaughter of the animal. There is no legally prescribed withdrawal time for any of the approved implants in the USA and Canada. Table 3 gives an overview of implanting strategies currently applied in beef production, recommended "re-implant windows", *i.e.* optimum re-implant times, and calculated "optimum payout periods", *i.e.* the time during which an implant releases growth promoter above an effective growth stimulating level. For maximum benefit, farmers and animal producers are advised to keep the level of implant growth promotant above the effective growth stimulating level until slaughtering." (footnotes omitted)

- At para. 31: "In the USA and Canada veterinary prescription is not compulsory for approved hormonal growth promoters. Supervision by a veterinarian is not required either. To the contrary, in both countries hormonal growth promoters are freely available in the over-the-counter sale as well as in self-service at agricultural retail stores and even by mail." (footnotes omitted)

- At para. 32: "Hormonal growth promoters are not approved for use in veal calves in Canada and the USA. There is nevertheless clear evidence that different hormones are being used in veal calves in both countries. A European Commission inspection mission to Canada in 1998, intended to evaluate the Canadian residue control system, reported that the CFIA had recently performed two special surveys to evaluate the possible misuse of trenbolone in veal calves. The surveys were carried out in compressed time periods using random samples and produced the following results: The first survey covered the period between June and July 1997 and produced 91 positive out of 281 liver samples taken (32.7%). The second survey covered the period from April 1997 through January 1998 and produced 85 positive out of 210 liver samples taken (40%)." (footnotes omitted)

- At para. 33: "The Canadian Food and Drug Act and Regulations do not define clearly extra-label or off-label use. The Canadian authorities accept, however, that a farmer may use authorized hormone implants in veal calves on condition that residues in liver and muscle comply with the so-called "administrative action levels" established for bovine tissues. In other words, the Canadian authorities tolerate the off-label use of hormone implants by farmers for growth promotion purposes and do not enforce the label instructions." (footnotes omitted)

- At para. 34: "In the case of the USA, two European Commission inspection missions in 1989 and 1990 had already revealed that hormone implants are also used in veal calves. The European Commission inspectors themselves found implants in the ears of two out of ten veal calves they examined; however, no subsequent action was taken by the national authorities. Furthermore in a letter from the Center for Veterinary Medicine of the Food and Drug Administration (FDA) to the American Veal Association of 29 December 1989 the FDA expresses its concern about the misuse of hormone implants in formula-fed veal." (footnotes omitted)

- At para. 35: "The most recent results of a study, which was commissioned by the European Commission as part of its complementary toxicological risk assessment of hormonal growth promoters and which was intended to determine the amount of hormone residues in US meat and offal, confirms the off-label use of hormonal growth promoters in the USA. First, although no hormonal growth promoter is

approved for veal calves, residues of trenbolone acetate and zeranol were found both in calf liver from the US domestic market and in calf samples from US meat consignments sampled at the border inspection points of the EU. Second, although melengestrol acetate (MGA) is only approved for use in heifers, a substantial number of the meat samples that tested positive for MGA residues were subsequently identified by DNA gender identification to stem from male animals." (footnotes omitted)[7]

- At para. 39: "A further violation of GVP related to off-label use of hormonal growth promoters was reported from Canada. The registration requirements for the use of melengestrol acetate (MGA), a growth promoter incorporated in the feed for heifers, stipulate that: "*MGA must not be fed to heifers treated with other hormonal drugs.*" Nevertheless, during the visit of a European Commission inspection team in 1998 to a Canadian feedlot, the feedlot operator declared that until recently his heifers were treated simultaneously with Synovex®, an approved implant containing testosterone and estradiol, and with MGA." (footnotes omitted)

- At para. 57: "Evidence on the existence of a black market for veterinary drugs and growth promoters in the USA and in Canada can be inferred from publications of the FDA's Center for Veterinary Medicine. These publications reveal that over the past years there has been a large-scale smuggling of illegal animal drugs, e.g. clenbuterol, from Canada into the USA." (footnotes omitted)

- At paras. 65 and 68: "In the USA a threshold level, utilisable for residue control programmes, has been established for only one of these six hormones, that is a tolerance level for melengestrol acetate. The other so-called "*safe concentrations for total residues in edible tissues*" established for trenbolone acetate and zeranol and the so-called "*increments*" established for the three endogenous hormones are not suitable for a residue evaluation by routinely performed examinations." and "It can, therefore, be concluded that in the USA only the tolerance limit for melengestrol acetate is appropriate to be used in a residue control programme." (footnotes omitted)

- At paras. 70, 71 and 73: "70. Despite clear provisions in the Food and Drug Act and Regulations on the general zero tolerance with certain well-defined exemptions, the Canadian authorities have adopted so-called "administrative action levels" for certain substances, including trenbolone, zeranol and melengestrol acetate, not listed in the Food and Drug Regulations. It has to be stressed that the application of the "administrative action levels" is not consistent with the Canadian Food and Drug Act. Although the "administrative action levels" are identical with the MRLs established by Codex it can be concluded that the Canadian authorities have not adopted legally enforceable threshold levels for the three approved synthetic hormones.", and that: "71. It has to be noted that these "administrative action levels" are applied also to veal calves, although the hormones in question are not authorised for this category of bovine animals.", and that: "73. It follows that the USA and Canada, with the exception for melengestrol acetate in the USA, either lack enforceable residue limits or cannot or do not enforce the ones they have." (footnotes omitted)

- At para. 81: "These findings have now been confirmed by the provisional results of the 1999 specific European Commission study on residue control of meat and liver imported from the USA under the Hormone Free Cattle Programme (HFC

[7] The recent study in question is Exhibit EC-53.

Programme). The available preliminary results of this study, based on US meat and liver samples collected at the border inspection posts of the EU, show that : "*In total it is concluded from this study that the HFC Programme is not effectively controlled by the responsible US authorities. From the residue findings the misuse of the US approved xenobiotic 'hormones' trenbolone, zeranol and MGA in this HFC Programme is shown in at least 12% of the samples. No definitive conclusions can be drawn from this study about the misuse in the HFC Programme of the US approved hormones (17β-)estradiol, testosterone or progesterone. However, for estradiol the misuse is indicated for at least one sample. No evidence has been found so far that in the HFC Programme other 'hormones' are used than those approved in the USA. HFC violative products were exported to the European Union by 3 out of 4 different USA meat sellers sampled in this study.*" "(footnotes omitted)

- At para. 90: "It must be underlined that there are no specific regulations in the USDA Code of Federal Regulations on disposal procedures for implantation sites, e.g. for implants in the ears." (footnotes omitted)

15. Further concrete evidence that misuses or abuses are not exceptional occurrences in the US and Canada is provided at the following Exhibits:

- Exhibit EC-69, where in 2004 Guidance for Industry, the US FDA stated that "use of unapproved hormone implants in non-ruminating veal calves has occurred." Equally, Exhibit EC-70 for Canada.

- Exhibits EC-96 and 103, which although concern the unauthorised hormone DES in 1999-2000, do show that a black market also exists in the US for these hormones as well as for other hormonal substances. Moreover, Exhibit EC-69 contains several examples of misuse and black market activities in the US.

- Exhibit EC-102, which states, inter alia, that the US Food Safety and Inspection Services (FSIS) "is concerned about the widespread, illegal use of drug implants in young calves that was discovered in 2004". The same exhibit also states that "FSIS learned that the use of growth promoting implants was a widespread practice within the veal industry. However, the Food and Drug Administration has not approved growth promotion implants for use in food animals presented for slaughter as veal and considers their use to be a violation of the Federal Food, Drug, and Cosmetic Act". This example demonstrates that, contrary to what the US has been arguing before the Panel, abuse and/or misuse is a "widespread practice in the US veal industry".

16. It is, therefore, imperative that the US, instead of avoiding the discussion by arguing that the EC has based its evidence on unrealistic or hypothetical examples, to engage for once in a real discussion on the substance of the concrete evidence provided by the EC.

17. The US comment (at para. 13 of its reply of 18 October 2006) and Exhibit US-28 confirm the EC findings. Exhibit US- 28 confirms that the author of the NebGuidance (University of Nebraska) on re-implanting was himself confused and perplexed by the possible interpretation of the NebGuidance, as so many less-educated farmers would undoubtedly have been for so many years that they have been following it. He nevertheless agreed to propose to make revisions to it, but he still insisted that the corrections "should not be interpreted as a change in our recommendations."

18. Furthermore, it is important to note that the NebGuidance is not the only example of concrete evidence that recommends multiple re-implanting. Exhibit EC-17 explains on page 54 (with further citation of at least six scientific publications) that "the manufacturers' instructions provided with the preparations, for instance, do not contain any explicit warning against multiple application. Even in the scientific literature, repeated or multiple treatment of different combined preparations is often recommended to achieve optimal results (4-9)". The US has not replied nor has it ever contested the evidence contained in these scientific publications.

19. The same applies to Canada's comments. Exhibit EC-17 states on page 54 (with concrete reference to scientific literature) that: "Misuse of trenbolone acetate in calves was reported in Canada (10). According to that study, in 1996/97, 14% of 353 tested veal liver samples contained more than 2 ng trenbolone-17a/g, and 5% even more than 10 ng/g".

20. The US argues (at paras. 12 and 15 of its reply of 18 October 2006) that the EC has failed to provide any evidence that violative residue levels would result except in the most extreme overdosing. This is not correct. The 1999 SCVPH opinion contains Table 2 on page 35, which shows as regards oestradiol-17β that the level of residues concentration in lawfully treated animals according to GVP exceeds by several times the level of concentrations observed in untreated animals.[8] Moreover, the study by R. Stephany 2001 (AMPIS 109, 357-346) (see Exhibit EC-65, at page S357) found that **meat from the regular US market contains on average 7.5 times more estrogens than meat from untreated animals**. If the more recent data concerning the endogenous production by pre-pubertal children are taken into account, such treatment according to GVP already leads to the ADI being exceeded. It goes without saying that multiple implanting, which necessarily leads to higher concentration of residues, would inevitably exceed even further the recommended ADIs by JECFA.[9]

21. Contrary to the US statements (at para. 14-15), both Dr. Boisseau and Dr. De Brabander (to questions 45, 46, 48) have confirmed that if GVP is not respected, the ADIs and MRLs become useless and risks to human health are likely to occur.[10] Unlike the US argument (and the reply of Dr. Boobis to question 48), the EC has performed a qualitative assessment and a quantitative assessment (to the extent possible) of exposure to residues in meat from animals treated not in accordance with GVP, even if a qualitative assessment alone would have been sufficient (see section 3.3, pages 30-32 of the 1999 SCVPH, and Exhibit EC-73).

Q5. In its comments on comments of the United States and Canada on experts replies to the Panel questions (in particular Question 13), the European Communities indicates that oestradiol 17β might be a "weak genotoxin" (para. 44). At what doses is genotoxicity observable *in vivo*? How are these doses comparable to those found in meat from cattle treated with growth promoting hormones? How would this assertion affect the identification of adverse effects and the evaluation of potential occurrence of these effects from consumption of meat from cattle treated with oestradiol 17β for growth promotion purposes?

22. The EC contests the US argument (at para. 16) that the EC has presented "just one study" which addresses genotoxicity of estradiol-17β *in vivo*. The 1999 SCVPH contains already reference to one such study (at page 41, section 4.1.7). The EC provided four more studies which discuss genotoxicity *in vivo* on different animal tissues: see Exhibits EC-48, 118, 121 and 125. As regards Exhibit EC-125, the EC notes that the US has made incorrect assumptions (at paras. 17-18) that are

[8] The 1999 SCVPH opinion contains similar evidence for the other natural hormones.

[9] Another error of the US is to compare the level of residues resulting from treatment according to GVP with the level of circulating oestradiol-17β in pregnant cows. This is wrong because in the EC pregnant cows are not slaughtered for human consumption.

[10] Moreover, despite the US argument to the contrary, Dr. Boisseau stated (reply to question 50) that farmers have "a temptation to use these hormones in a way different from the approved ones."

inconsistent with the data provided by the EC, based on a substantial literature published over the last 3 decades regarding the use of Silastic capsules to administer hormones to experimental animals and women. The implant in Silastic capsules for women was marketed as being effective for up to 5 years due to slow release of the steroid when it is packed into a capsule. As the EC pointed out, the daily release rate from a Silastic capsule used in the *Cavalieri et al.* study containing a total of 5 mg oestradiol, that is intended for long-term studies and steady-state release over a long period of time, is about 1 microgram/kg/day. Clearly, the US assumption that the entire amount of oesttradiol-17β in the capsule (5 mg) is released each day cannot be correct. Another issue is that the US response assigned a weight to rats of 250 mg, which is the weight of a very young rat, and would not be the weight of a 6-7 months old rat by the end of a study, in which the oestradiol-17β was administered to adult rats for 140 days, as was done in the *Cavalieri et al.* study. In this regard, the EC estimate of a weight of 330 g is very conservative. Since the dose per day is expressed relative to body weight, by assuming an unrealistically low body weight, the US is attempting to make it appear that the daily administered dose is higher than it really is. When this is taken together with the invalid US assumption that a Silastic capsule releases the entire amount loaded into it each day (which would require it being refilled each day), it is clear that the US calculations of the oestradiol-17β doses that result in mutagenesis are profoundly flawed. As the EC has explained with its reply of 18 October 2006, the mutagenic effect in Exhibit EC-125 was brought about at a dose which is potentially within the 1000-fold safety margin established from the lowest observed adverse effect level (LOAEL) on which JECFA's ADI is based.[11] Therefore, the dose at which *in vivo* genotoxicity was observed was not "astronomically higher", nor "exponentially greater", nor "massive", as the US (and Canada) has wrongly argued. Quite the opposite, it is **not higher** than the dose normally used in experiments for the approval of chemical substances internationally.

Panel Questions to the United States and Canada:

Q18. Would you consider that, for the purpose of the DSU, Directive 2003/74/EC should be viewed as a new measure or as the continuation of the previous measure found to be inconsistent with the WTO Agreement, since it still imposes a ban?

23. There can be no doubt that following the DSB's rulings and recommendations a measure has been taken by the EC to comply with. For the purposes of the DSU, therefore, there exists a new measure.

24. First, Directive 2003/74/EC unquestionably *is* a new measure in that it came out of an entirely new legislative process, involving both the European Parliament and the Council of the European Union as legislature. Second, the measure is by no means identical to the previous measure. It for the first time enacts a provisional ban with regard to all substances but oestradiol-17β, further restricts use for therapeutic and zootechnical purposes and abolishes all other exemptions. Third, and most importantly, the new Directive is obviously based on a risk assessment taking into account the most recent scientific evidence available.

25. Whether this new measure successfully implements the rulings and recommendations of the DSB is a different question. Both Canada and the United States seem to argue that it is the only question that matters for the purposes of assessing whether they are entitled to continue the

[11] The US attempts (at footnote 13 of its reply of 18 October 2006) to diminish the importance of the *in vivo* studies performed with catechol metabolites and refers to an alleged statement of Dr. Metzler, which he has not made. The important point about catechol metabolites in treated meat is to note what Dr. Guttenplan has said (with his reply to question 17), namely that the small amount of catechol metabolites detected in meat from treated animals is explained by the fact that "cattle do not efficiently metabolize estradiol to catechols", and that "the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity".

suspension of concessions. In the European Communities' view it is not. In the presence of an obviously new measure that has been adopted in a transparent and good faith effort to implement the DSB rulings and recommendations, Article 23 DSU triggers an obligation on the original complaining parties to assess that new measure, to bring a 21.5 proceeding if they take the view that the measure does not achieve compliance (and) or (to suspend) to cease the suspension of concessions. The latter obligation results from the fact that there is no multilateral determination that the new measure violates or continues to violate WTO obligations. It follows that the burden is on the US and Canada in the first place to demonstrate that the EC has not solved the nullification or impairment through the new measure once notified to the WTO. Indeed, having followed an open and transparent procedure for the elaboration and adoption of the new measure, having notified it in accordance with the provisions of the WTO/SPS Agreements, and having given the defending members the opportunity to submit their comments all along, it is reasonable to argue that the burden is on them to establish that the new EC measure does not solve the nullification or impairment. Any other interpretation would be unreasonable and would go against the object, purpose and structure of the WTO Agreements because it would enable recalcitrant WTO members to unlawfully affect international trade almost indefinitely.

Panel Questions to the United States:

Q19. Does the United States argue a violation of Article 5.2 and of Article 5.6 SPS? In other words, do you expect the Panel to issue findings regarding the compliance of Directive 2003/74/EC with those provisions? What is the purpose of the reference to Article 2.2 SPS in para. 27 of the US rebuttal submission?

26. The European Communities takes note of the United States' reply that the Panel would be required to look only at Articles 3.3, 5.1 (including an examination of Article 5.2) and 5.7.

27. Moreover, as the EC has explained above with its comments on the US reply to question 2, the US is wrong to argue that the EC has not based its measure on a risk assessment within the meaning of Article 5.1 and 5.2 SPS. The EC did conduct such a risk assessment not only for oestradiol-17β but also for the other five hormones. But for the reasons explained several times to the Panel, it could not complete the risk assessment for the five hormones because of the insufficiency of the relevant information and the important gaps in our scientific knowledge. That is why it had to base its measure on Article 5.7 SPS. It should be noted that Article 5.1 SPS provides that the measure is based on an assessment "as appropriate to the circumstances", and Article 5.7 states that a more "objective" assessment of risk would be performed once the missing pertinent information is obtained.

Q20. Could the United States clarify whether its arguments regarding a violation of Article 3.3 SPS apply only in relation to the definitive ban on oestradiol 17β or whether they apply also in relation to the provisional ban imposed on the other five hormones?

28. The European Communities would like to recall what it has understood to be the United States representative's statement at the second substantive hearing. Mme Orozco had asked which Codex Alimentarius standards the United States was relying on for the purposes of its Article 3.3 claim. In reply to this question the United States representative referred only to the standards adopted for testosterone, progesterone, zeranol and trenbolone acetate. No mention was made of the standard for oestradiol-17β.

29. Moreover, the US states (at paras. 27-28) a number of times that it has demonstrated that the EC has failed to provide a scientific justification. The EC does not agree that the US has managed to discharge its burden of proof.

EC Questions to United States and Canada:

Q1. Please explain, if possible in detail, what kind of scientific evidence on exposure-assessment from residues in meat treated with the six hormones for animal growth promotion was used by the United States and Canada when these substances were authorised? Was this exposure assessment a quantitative one? Please provide concrete reference to studies used in your exposure assessment and, if possible, to those of JECFA for the six hormones in question (in case you know the references).

30. The US states (at para. 3 of its 18 October 2006 reply) that the US FDA "required the sponsors to conduct extensive residue studies". These residues studies have never been published and the EC has never been given a copy fro review, whereas the US has had access to the more recent (same or similar) studies conducted by the EC.

31. The US reply (at para. 5) confirms that the US FDA did **not** establish an ADI for the three natural hormones. Most importantly, it also confirms that no extensive toxicological testing in experimental animals has been performed. In other words, it confirms that the US has not performed the full battery of toxicological testing in order to decide whether these hormones are carcinogenic and/or genotoxic. It also confirms that the "permitted increased daily exposures" set by the US FDA are based on the assumption – and no more than an assumption – that "the amounts of these hormones present in edible tissues of treated cattle were found to be very small relative to the endogenous production in humans". In other words, the US admits that it has not carried out the kind of quantitative exposure assessment of residues in hormone-treated meat, which it now accuses the EC for not having performed. The reality, therefore, is that the US "*permitted increased daily exposures*" are based on simplistic and scientifically unsound extrapolations and assumptions, not on sound scientific experiments.

32. The US refers (at para. 6 of its reply of 18 October 2006) to the "exposure assessment conducted by JECFA", thus again admitting implicitly that it has itself not conducted such an exposure assessment from residues in hormone-treated meat. However, as the EC has explained several times to the Panel, JECFA has not conducted such an exposure assessment either. What JECFA has done so far was to review the old residues depletion studies from the 1970s provided to it confidentially by the US pharmaceutical industry (see e.g. Exhibits CAN-17 for the three natural hormones and the similar studies for the other three synthetic hormones) and established the ADI on the basis of assumptions, extrapolations and safety factors. But the EC has also performed and made available to the public residues depletion studies for all these hormones similar to those used by JECFA. Moreover, the EC has in addition made an exposure assessment, which Dr. Guttenplan explained in his reply to questions 52 and 55, as follows: "calculations are presented (EC rebuttal. Para. 122) that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen exceeding the daily production rate of oestradiol in pre-pubertal children". The US reply shows that it has not done so.

33. Finally, the US and Canada's replies cannot hide behind the argument that JECFA has performed a quantitative exposure assessment, because the data claimed to be used by JECFA are the same data of the 1970s provided by the pharmaceutical industry during the authorisation procedure in the US.

Q2. Please indicate, if possible in detail, whether your risk assessments, and if you know those of JECFA, of the six hormones in question for animal growth promotion have attempted to calculate the risk to humans from the additional exposure resulting from the residues in hormone-treated meat when used according to GVP and when GVP is not respected. Was it a quantitative exposure assessment? If so, please provide the precise reference to the data. (Please note that we are not referring here to residue-depletion studies contained in CAN Exhibit-17,

since the EC has also conducted such residues depletion studies for its 1999-2002 risk assessments).

34. The US reply (at paras. 7-12) confirms once again, as explained above, that the US has not attempted to calculate itself the risk to humans from the additional exposure to residues from hormone-treated meat. It refers to the JECFA monographs, which do not contain an exposure assessment, which is not different from that performed by the EC, with the notable difference that the EC's assessment is based on more recent, publicly available and peer-reviewed scientific data.

35. The same comment applies to the reply of Canada. Canada forgets that exposure to background (endogenous) levels alone of the natural hormones has already found to cause cancer in humans and inappropriately assumes, like JECFA, that the additional exposure from the residues in meat would not increase the risk. Canada, like the US, forgets that the EC has demonstrated (see, e.g., the study by R. Stephany 2001, AMPIS 109, 357-346, Exhibit EC-65) that meat from the regular US market contains on average 7.5 times more estrogens than meat from untreated animals and that, even without misuse, the ADIs established by JECFA will be exceeded if the most recent values of endogenous production by pre-pubertal children is taken into account.

Q3. The EC understands that some of the experts (Drs. Guttenplan, Sippel and Cogliano) have stated that it is not possible to determine with accuracy the dose-response curve at the very low levels of exposure from these hormones in general and when used for animal growth promotion. Do you agree with these statements? If not, could you please provide the precise references to scientific studies where this has been done? What would be the implications of this impossibility for the need to perform a quantitative or qualitative exposure assessment for these hormones when used for animal growth promotion?

36. The EC notes first that the US does not correctly represent (at para. 14 of its reply) the statement by Dr. Guttenplan at the meeting of the Panel with the experts. In that meeting, Dr. Guttenplan stated (as did three other scientists) that, in his view, there will be a risk (which will be not zero but a small one) caused from the residues in meat from animals treated with these hormones for growth promotion. The same applies to the comment by Canada (at para. 9 of its reply).

37. Furthermore, the US gives credit to the statement by Dr. Boobis that the "carcinogenic effects appear to be a consequence of its endocrine activity", when the US admits that no long-term carcinogenicity studies have been performed when it approved these hormones for growth promotion.

38. Furthermore, Canada argues (at para. 10 of its reply) that the statements by Dr. Sippel and Dr. Cogliano "must yield to the expert advice of those who are qualified to evaluate actual carcinogenic potential at low doses". However, Canada forgets that both Dr. Boisseau and Dr. Boobis are the same persons who have participated in the elaboration of the JECFA report and, moreover, Dr. Boisseau admitted that he has never carried any toxicological experiment with these hormones himself.

Q4. If you were to agree that scientists cannot define the dose-response curve as explained in the previous question, would this state of scientific knowledge be defined as "scientific uncertainty" in this area? If not, please explain.

39. The US reply (at paras. 15-16) is another distraction by referring to "theoretical risk", when the scientists agreed that the dose-response curve at low dose in the case of these hormones cannot be defined. Moreover, given that in the calculations of the US and JECFA the existence of a threshold below which adverse effect is alleged not to occur is a basic assumption, the EC question does not pertain to a theoretical risk but to a very real and undisputed one. The US and Canada (like JECFA) have not managed to explain how is it possible to establish a no hormonal effect level when the

scientists ignore the real dose-response curve of these substances when used for growth promotion purposes.

40. In addition, Canada places (at para. 12) on the same side Drs. Boobis, Boisseau and Guttenplan, when the latter clearly stated in the hearing that the risk from residues in hormone-treated meat is small (but not zero) and Dr. Boissaeu admitted that he has no specific knowledge as he has never carried any experiment with these hormones.

Q5. Could you please explain what is your position on the existence or non existence of an international standard for MGA for the purposes of Articles 2, 3 and 5 of the SPS Agreement in these disputes?

41. Canada argues that "other agencies and health authorities have conducted similar assessments and have come to the same conclusion", but fails to mention which are these other agencies and authorities nor does it provide copy of their assessments. If Canada implies that these other authorities are the agencies of the US and Canada, the EC would be very happy to receive copy of their assessments and the underlying studies on which they are based for review. Indeed, the EC urges Canada to submit such assessments, if they really exist, to the Panel for review.

EC Questions to the United States:

Q1. The 2002 US Report on Carcinogenesis (Exhibit EC-101) states inter alia that: "veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food producing animals to above their normal levels" (p.8). How do you reconcile this with your proposition in para. 51 of your First Written Submission?

42. The EC notes that the US is selectively quoting figures for different (male or female) animals and at different physiological state (pregnant or not) is order to sustain its claim that the residues are within the range of naturally observed levels. However, the US does not discuss the other evidence presented by the EC showing that **meat from the regular US market** contains on average 7.5 times more estrogens than meat from untreated animals (see Exhibit EC-65, at page 357, and the tables 2, 5 and 7 of the 1999 SCVPH opinion). Furthermore, the US keeps comparing the residues from treated animals with the levels of residues in pregnant cattle, when the EC has explained to the Panel that such pregnant cattle are practically not slaughtered for human consumption in the EC.[12] Pregnant cows, therefore, are not the appropriate comparator.

Q2. What was the reason to conclude for the first time in the 2002 US Report on Carcinogenesis that estrogens (including oestradiol-17β) are carcinogenic not only by receptor-mediated effects but that in addition there are possibly by direct and indirect genotoxic mode of action? Was it because of new developments in scientific research that became available after 1999?

43. The EC considers that the US reply (at para. 22 and footnote 14) confirms that oestradiol-17β has moved from "reasonably anticipated to be human carcinogen" in 1985 to be listed for the first time in 2002 as "known to be a human carcinogen". Moreover, the 2002 US RoC links for the first

[12] In any case, the US argument is also factually not entirely correct because **Table 2** of the 1999 SCVPH opinion (at page 35) provides data showing that the concentration of E2 (oestradiol-17β) residues in muscle of treated heifers (30 days) according to GVP are slightly higher (33.2 ng/kg) than the values for untreated pregnant heifers (32.7 ng/kg). The same applies to fat tissue, 86.7 ng/kg in treated heifers compared to76.5 ng/kg in untreated pregnant heifers, whilst the values for kidney are not substantially different. Moreover, the EC has shown that misuse or abuse of these hormones leads inevitably to much higher concentration of residues in treated meat.

time the risk of cancer to residues in meat from animals treated with this hormone for growth promotion. The US claims (at paras. 23-24) that the 2002 US RoC is not evidence of a risk from meat from cattle treated with estradiol for growth promotion. However, the US cannot make this claim because it has not performed the necessary experiments **after** the 2002 RoC has declared oestradiol-17β a proven human carcinogen by direct genotoxic action. All the assessment which the US claims to have performed for these hormones for growth promotion date from the 1970s. Conversely, as the replies of Dr. Cogliano and Dr. Guttenplan to Panel question 26 have established, the data used by the EC to establish such an association are "at least consistent with a possible effect of hormones on breast and prostate cancer". Therefore, the US has failed to provide better evidence to the one used by the EC.

Q3. The 2002 US Report on Carcinogenesis states inter alia that: "The RoC does not present quantitative assessments of the risks of cancer associated with these substances. Thus listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives. Such formal risk assessments are the responsibility of the appropriate federal, state, and local health regulatory and research agencies." If so, have the competent US authorities made the quantitative assessment of the risks of cancer posed by the residues of six hormones in meat from animal treated for growth promotion? If not, when are you going to do it?

44. The EC notes that the US has carefully avoided (at para. 25) to reply to this crucial question. Hopefully the Panel will be able to draw, to the extent possible, the necessary inferences.

45. The US statement (at para. 26) inappropriately downplays the importance of evidence coming from epidemiological studies. In any case, the 2002 US RoC is not based only on epidemiological evidence, but also on the reported results from toxicological and carcinogenicity studies, as is the paper by Professors Liehr and Yager mentioned therein to demonstrate direct genotoxicity.

46. The US for the first time admits (at para. 27) what the EC has always been arguing, namely that:

> "assessment of the risks to human health associated with the use of sex steroids in food-producing animals presents unique challenges due to the fact that exposure to the compound occurs against a background level of endogenous production in all segments of the population".

47. As the EC mentioned above with its comments on the US reply to question 1 from the EC, the US has not conducted extensive toxicological testing, as should have done, and based its "permitted increased exposure" on pure assumptions and simplistic extrapolations. Indeed, the US assumed that residues in hormone-treated meat would add very little to the endogenous production by humans. But the US assumption ignores the fact that exposure to background (endogenous) levels of oestrogens already causes cancer in humans and any further addition to such exposure from exogenous sources is going inevitable to increase the likelihood of causing cancer. This is all the more so since the scientists do not know what is the dose-response curve from low exposure to these hormones in order to establish a safe threshold.

Q4. The 2002 US Report on Carcinogenesis states inter alia that: "Estimating the extent to which listing a substance in the RoC protects public health is perhaps the most difficult task in preparing the RoC. The carcinogenic risk (i.e., the probability of developing cancer) depends on many things, including the intensity, route, and duration of exposure to a carcinogen. People may respond differently to similar exposures, depending on their age, sex, nutritional status, overall health, genetics, and many other factors. Only in a few instances can risk for cancer be estimated with complete confidence, and these estimations require studies of long-term human

exposures and cancer incidence in restricted environments, which rarely are available." Despite this recognition of the difficulties, could you please explain if you have nevertheless performed the long-term human exposures to the residues of these hormones in treated-meat in order to quantify if they pose a risk to human health? Do you know if JECFA has performed such a specific quantitative dose-response assessment?

48. The EC argues that the above-mentioned quotation from the 2002 US RoC confirms its arguments that a quantitative exposure assessment is not really possible and the US (and Canadian) criticism in this regard is unfounded.

Q5. In relation to para. 8 of the US statement of 3 October please explain if you have now made a determination? If not, what does it mean "being in the process of reviewing? What are you doing exactly? Since the EC's risk assessment dates of 1999 (and reviewed and confirmed in 2000 and 2002), how long is your review process going to take? Is there any information that the US is now missing? Is there any mechanism by which the US will complete its review within a reasonable period of time now?

49. The EC considers that the US reply confirms that it has not yet completed its review and, apparently, is not likely to complete it any time soon.

Q6. The US stated that the risk assessments performed by JECFA must be presumed to be in compliance with Article 5.1. of the SPS Agreement. But the risk assessments performed by JECFA for these hormones for animal growth promoters do not contain the kind of quantitative or qualitative exposure assessment that Canada and the US criticise the EC for not having done. Nevertheless, the US and Canada appear to assume that JECFA's assessments are consistent with Article 5.1. SPS. Please explain why under these circumstances would the EC's risk assessment be inconsistent with Article 5.1. of the SPS Agreement.

50. The EC notes that the US provides a general reply without any arguments nor specific reference to the documents showing that JECFA did the kind of exposure assessment which the US accuses now the EC for not having performed. As the EC has explained several times (see, e.g., EC Oral statement of 3 October 2006, at paras. 4-5), the kind of quantitative exposure assessment, claimed to have been done by the defending members, cannot be performed.

<u>EC Questions to Canada</u>:

Q1. In relation to your example for the oestrogen level in pregnant women (para. 53 of your Oral Statement) could you please comment on Exhibit EC-56 where there is evidence that *in utero* exposure to oestradiol has given rise to a number of abnormalities and suspected of an increased rate of cancer? Assuming that this finding is related to the low-dose response uncertainty, do you have any evidence that the 2ng added to endogenous oestrogens production are not likely to have any such effect?

51. The EC notes that Canada's reply is typical of the unscientific assumptions and simplistic arguments it has been making all along in this dispute. The EC does not pretend to have found the ultimate truth. The study in Exhibit EC-56 builds on existing scientific literature which postulates that "the risk of breast cancer is influenced by hormonal exposure *in utero*". This proposition is not new (see the first five references to scientific literature provided in Exhibit EC-56). The EC study provides further support to existing scientific evidence.

52. The simplistic argument of Canada is to state that "as a result of the homeostatic control mechanism, endogenous production is adjusted to take into account exogenous exposure. Thus, the low dose exogenous oestradiol to the mother does not translate into low dose to the foetus." The point

is that Canada has no scientific basis to make the simplistic assumption that the adjustment will take place or that it will take place in all cases. Equally, Canada has no scientific basis to argue that a 2ng added to endogenous oestrogens production are not likely to have any adverse effect. All the EC is saying on this point is that we do not know, and Canada knows no better. But what we do know is that the experiment in question provides further support to existing evidence that hormonal exposure *in utero* influences the risk of breast cancer. Canada obviously does not believe that exposure to low level of residues in treated meat is likely to cause cancer. But this belief is based on mere intuition, not scientific proof, because the experts of the Panel have confirmed that the dose-response curve from low exposure cannot be established for these substances.

Q2. As regards the reference to Carbadox (see para. 67 of Canada's oral statement of 3 October): Could you please explain briefly what happened and what were the reasons for which you have changed your risk assessment for Carbadox? Was it simply on the ground that Carbadox was found to be genotoxic or was it because you have carried out before a quantitative or qualitative exposure assessment for the residues in pork meat treated with Carbadox?

53. The reply of Canada avoids addressing the crucial point, namely why did it need almost ten years to admit what the EC has been arguing since 1996, namely that the metabolites of Carbadox are carcinogenic and genotoxic. What Canada calls now "new information" was available at the time of the first hormones panel in 1996, where Canada was still authorising Carbadox and was strongly arguing that the EC has been acting inconsistently. If Canada is willing to keep making the same kind of mistake for these hormones as it did for Carbadox at the time for the sake of some small economic benefit, the EC is not prepared to sacrifice its high level of health protection.

ANNEX C-3

REPLIES OF CANADA TO QUESTIONS POSED BY THE PANEL AFTER THE SECOND SUBSTANTIVE MEETING

(18 October 2006)

Questions to all parties:

Q1. With reference to the statement by the European Communities, *inter alia* in para. 12 of the EC reply to Question 3 of the United States, do the parties consider that a Panel is entitled to address "systemic claims" or issues related to "systemic obligations" and, if so, to what extent?

1. The Panel has been asked to determine whether Canada and the United States acted contrary to Articles 23.1 and 22.8 of the *DSU* by continuing to suspend concessions after the EC claimed compliance. Part of such a determination is a determination of whether the EC's measure originally found to be non-compliant has been "removed". The EC's distinction between its "systemic claims" and its "direct claims" reflects the distinction between its claim that its measure should be presumed to have been "removed" (*i.e.*, brought into compliance) and its subsequent arguments that it has actually brought its measure into compliance. By addressing whether the EC's unilateral claim of compliance is sufficient to satisfy Article 22.8, the Panel will be addressing the EC's so-called "systemic claims". Canada has already argued in its various submissions that the EC's unilateral declaration of compliance is insufficient to satisfy the requirements of Article 22.8, and therefore there is no merit to the EC's "systemic claims". It is only by having the Panel confirm that it has, in fact, complied (*i.e.*, its "direct claims") that the EC can prevail on its claims against Canada and the United States.

Q2. With reference to the US rebuttal, para. 27, do the parties consider that a measure that does not comply with the requirements of Article 5.7 SPS would automatically be in breach of Article 2.2 SPS, or Article 5.1 SPS, or both?

2. Canada agrees with the statement by the United States in paragraph 27 of its Rebuttal Submission that, because the EC's ban fails to meet the requirements of Article 5.7, the EC is not exempt from satisfying its obligations under Article 2.2 and Article 5.1.

3. However, Canada does not read this statement as implying that a failure to comply with Article 5.7 "automatically" leads to a breach of Articles 2.2 and 5.1, in a legal causative sense. As the Appellate Body in *Japan – Agricultural Products II* stated, Article 5.7 operates as a qualified exemption from the obligation under Article 2.2 not to maintain SPS measures without sufficient scientific evidence.[1] A failure to satisfy the requirements of Article 5.7 technically means that the qualified exemption from the obligations in Article 2.2 does not apply.

4. That being said, if a Member claims that its SPS measure is consistent with Article 5.7 on the basis that relevant scientific evidence is insufficient to conduct a risk assessment, the Member is implicitly acknowledging that its SPS measure is maintained without sufficient scientific evidence. Were it otherwise and sufficient scientific evidence exists to maintain an SPS measure, then it follows that the relevant scientific evidence is sufficient to perform a risk assessment and Article 5.7 would not apply. If, having claimed consistency with Article 5.7, a Member fails to satisfy the first and second requirements of Article 5.7, it is difficult to envision how the Member can also comply with its

[1] *Japan – Measures Affecting Agricultural Products*, Report of the Appellate Body, WT/DS76/AB/R, adopted March 19, 1999, at para. 82.

obligations of Article 2.2. In such circumstances, the failure to comply with the requirements of Article 5.7 would imply a breach of Article 2.2.

5. Similarly, if a Member claims that relevant scientific evidence is insufficient to enable the performance of a risk assessment, the Member is, in effect, conceding that it is unable to comply with Article 5.1. If the Member fails to satisfy the requirements of Article 5.7, then the Member will have, in effect, breached Article 5.1 with no valid justification.

6. In this case, it is not necessary for the Panel to determine the precise legal relationship between Articles 2.2, 5.1 and 5.7. Here, the Panel's task is straightforward. The EC claims that it now complies with the recommendations and rulings of the DSB. In terms of the five provisionally banned hormones, the EC seeks to demonstrate compliance with the recommendations and rulings by showing that its ban is consistent with Article 5.7, not Article 5.1. By resorting to Article 5.7, the EC acknowledges that its provisional measures are not based on a risk assessment as required by Article 5.1, but claims that its measure nonetheless complies with the DSB recommendations and rulings because it is consistent with Article 5.7. Thus, consistency with Article 5.7 acts as an exemption from the obligation in Article 5.1. However, as the experts advised, the relevant scientific evidence is sufficient to enable the performance of a risk assessment. As a result, the EC is unable to satisfy the first requirement of Article 5.7 and therefore is not exempt from complying with Article 5.1. As the EC has conceded that its measure is not based on a risk assessment by claiming consistency with Article 5.7, the EC is unable to demonstrate compliance with the recommendations and rulings of the DSB.

Q3. When and how was each of the following documents made available to Canada and the United States? Please answer independently for each of the documents mentioned below:

(i) 1999 Opinion;
(ii) 2000 Opinion;
(iii) 2002 Opinion;
(iv) each of the "17 studies".

7. The 1999 Opinion was made available to Canada and transmitted by letter of May 1, 1999 from the European Commission.

8. Canada is unable to indicate when exactly the 2000 Opinion became available to it.

9. It is clear from e-mail correspondence between the Canadian Mission to the EC and the European Commission in April 2002 that the 2002 Opinion was available to Canada shortly after its adoption.

10. Following the release of the 2002 Opinion, Canada, through its own efforts, obtained copies of most of the published papers that were based on the 17 Studies and that were publicly available in 2002 or became publicly available relatively soon thereafter.

11. As part of the EC's response to Panel Question 16 (following the First Substantive Meeting), on October 3, 2005, the EC filed as Exhibits a large number of documents that were part of the 17 Studies. These EC Exhibits were subsequently renumbered and are now known as Exhibits EC-7A to EC-60 (inclusive). Of these Exhibits, the following were not published and therefore not available to Canada before October 3, 2005: EC-7A, 7B, 10, 29, 30A, 30B, 30C, 50, 51A, 51B, 51C, 52A, 52B, 53, 54, 55A, 55B, 56, 57, 58, 59 and 60. Exhibits EC-39, 40 and 41 were published in 2004 but only came into Canada's possession when filed as Exhibits by the EC in October 2005. Canada has

nonetheless reason to believe that the material available to it to date still does not constitute the complete record of the 17 Studies.[2]

Q4. Has the European Communities assessed in a systematic manner the existence and level of risks from failure to observe good veterinary practices with respect to the administration of oestradiol 17β as a growth promoting hormone to cattle, in particular in the United States' and Canada's markets? If so, please indicate where this assessment is to be found in the evidence provided to the Panel.

12. The EC has not assessed, let alone in a systematic manner, the existence and level of risks from failure to observe good veterinary practices with respect to the administration of oestradiol 17β as a growth-promoting hormone to cattle in Canada. In its Rebuttal Submission, at paragraphs 107 to 109, the EC appears to claim that the SCVPH assessed the risks associated with misuse and abuse of growth-promoting hormones and refers in its footnotes to various documents that purportedly support this claim. However, as Canada explained in its Comments on the EC Comments on the Answers by the Experts[3] and in Canada's Oral Statement at the Second Substantive Meeting (Legal Arguments)[4], none of these documents evaluates the potential adverse effects from misuse and abuse in Canada, taking into consideration the factors set out in Article 5.2 of the *SPS Agreement*. Accordingly, the EC has failed to perform a risk assessment appropriate to the circumstances in relation to alleged misuse and abuse in Canada.

13. In paragraph 108 of its Second Written Submission, the EC refers in a footnote to a "draft" "working document" that purports to be an assessment of risks arising from abusive use and difficulties of control of hormonal growth promoters.[5] The EC has failed to clarify the actual status of this "draft" "working document". The 1999 SCVPH Opinion only briefly refers to this document in its cursory analysis of exposure considerations in situations of misuse.[6] Notably, the EC failed to disclose this document in its response to Panel Question 16 (following the First Substantive Meeting), which requested that the EC identify all documents that comprise its risk assessment of the hormones in question. Indeed, to Canada's knowledge, the first time this "draft" "working document" was made public was in the EC's Second Written Submission, well after the EC claimed that Canada was in breach of its WTO obligations for refusing to accept the EC's unsubstantiated assertion that it had complied with the recommendations and rulings of the *DSU* – hardly consistent with the EC's claim that it has been fully transparent in relation to its data and scientific analysis.

[2] For example, Canada notes that under the rubric of Study 6 ("Analysis of 500 Samples for the Presence of Growth Promoters") the EC filed only Exhibit EC-19, which is a very short article by Dr. Rainer W. Stephany, entitled "Hormones found in Meat Samples from Regular Controls within the European Union and from US Imports". By comparison, another article by Dr. Stephany, entitled "Hormones in meat: different approaches in the EU and in the USA", which was filed by Canada as Exhibit CDA-12, refers in references 25 and 26 to interim reports by Dr. Stephany and Dr. F. André that are apparently part of Study 6. Reference 25 reads as follows: "Stephany RW, André F. (rapporteurs) Results of "hormone" residue analyses of bovine meat and liver imported into the EU and originating from the USA "Hormone Free Cattle Program" [,] First Interim Report, CRL document 389002 091, May 1999, Bilthoven, The Netherlands, 34 pp." Reference 26 reads as follows: "Stephany RW, André F. (rapporteurs) Results of "hormone" residue analyses of bovine meat and liver originating from the USA domestic market, Second Interim Report, CRL document 389002 093, June 2000, Bilthoven, The Netherlands, 38 pp." This suggests that Exhibit EC-19 does not present the complete results of Study 6.

[3] Canada's Comments on EC Comments, July 12, 2006, at paras. 94-108.

[4] Canada Oral Statement, October 2 and 3, 2006, at paras. 71-78.

[5] EC Second Written Submission, fn. 81, Exhibit EC-73 (formerly EC-17).

[6] 1999 SCVPH Opinion, at pp. 30-32 (Exhibit CDA-2). The "draft" "working document" is not attached as an Annex to the SCVPH Opinion.

14. In any event, Canada has already explained the flaws and deficiencies in the EC's purported assessment of risks of misuse. It is sufficient here to reiterate the most glaring deficiencies in its purported risk assessment.

15. The EC claims that the SCVPH Opinion's findings are "based on realistic conditions of use".[7] This leads the EC to conclude that "abuses or misuses of these hormones … are not uncommon" in Canada and the United States.[8] This claim is simply absurd. Not only does the EC fail to present any evidence of misuse and abuse in the feedlot beef industry, for which the hormones have been approved, the EC actually ignores evidence that conflicts with its desired conclusion. The findings are in fact based on erroneous assumptions and imagined worst-case scenarios that bear no relationship to realistic conditions of use. Here are a few examples:

16. First, the EC assumes that there are economic incentives to misuse approved products. As Canada has explained, this is simply not the case. Implants have been calibrated to provide an optimal dose.[9] Overdosing has a negative impact on growth performance, marbling of fat and carcass grade quality and likely increases negative behaviours in animals. Contrary to the EC's self-serving assumptions, cattle farmers in North America, where growth promoters are legal, stand to lose money from misusing these hormones.

17. Second, the EC relies exclusively on the reported misuse of trenbolone acetate in the veal industry in Canada in the late 1990s to support its claim that there is more general misuse and abuse. However, growth-promoting hormones have never been approved for the veal industry, a small specialty industry in Canada. Consequently, any misuse that has occurred in the veal industry cannot be extrapolated to those sectors of the industry for which growth-promoting hormones have been approved (*i.e.*, feedlot beef cattle). As is the case in Europe, where a product is not approved for use, there may be economic incentives for operators to engage in illegal use, because <u>any</u> use is prohibited. But this does not imply that misuse and abuse occurs where hormones have been approved for use under specific conditions. Tellingly, the EC fails to present any evidence that approved implants are being improperly administered in the beef industry in Canada. Moreover, in its analysis of reported misuse of trenbolone acetate in the veal industry, the EC conveniently ignores relevant residue testing data. These data show that, even in the limited number of cases where a residue was detected, the amount of residue for the most part never exceeded the MRL. Consequently, even where misuse occurred, residues were within the safe thresholds established by Codex.

18. Third, the SCVPH speculates about the possibility of misplaced implants. However, the labelled instructions for the administration of hormones are clear: the implants containing the slow-release pellets are to be injected subcutaneously in the animal's ear and the ear is to be removed from the food chain at slaughter. Out of the literally millions of cattle slaughtered every year in Canada, the only evidence presented to support the speculative claims of misplacing implants is a single finding reported by Canadian authorities back in 1998 of trenbolone residues in veal calves which were attributed to either "misplaced implants or from illegal treatment via intramuscular injection."[10] As is the case in Europe, where a product is not approved for use, operators engaging in illegal use have incentives to use clandestine methods of administration, such as intramuscular injections, in order to

[7] EC Second Written Submission, at para. 108.

[8] *Ibid.*

[9] See letter from Dr. Dee Griffin, University of Nebraska, to Dr. Adele Turzillo, FDA Center for Veterinary Medicine, October 20, 2005 (Exhibit US-28).

[10] European Commission, Assessment of Risks of hormonal growth promoters in cattle with respect to risks arising from abusive use and difficulties of control, Draft Report by special working group of external private experts and European Commission officials, Brussels, 29 April 1999, at p. 10 (Exhibit EC-73, formerly EC-17).

avoid detection. There is no reason to use such clandestine methods if the product is approved for use and used properly.

19. Fourth, the EC selectively ignores evidence that contradicts its fundamental premise. The EC fails to take into account what is arguably the most pertinent and direct evidence concerning misuse and abuse of hormones in Canada, namely, the results of on-going random and suspect testing conducted under Canada's official National Chemical Residue Monitoring Program. The results of this monitoring program are provided annually to authorities in EC Member States. That the EC has ignored this evidence is not surprising given that, far from supporting the EC's speculative assumptions, it manifestly contradicts them.

20. Fifth, the EC fails to take into account inspection and control procedures at federally inspected slaughterhouses. The EC twists examples of successful detection of non-compliance into a systemic failure of controls. On this logic, as EC authorities have detected numerous examples of misuse and abuse in Europe, the EC's complete ban on the use of growth-promoting hormones, and the control measures adopted to enforce that prohibition, have been an abject failure. Without analyzing the frequency of non-compliance, arguments of this nature say nothing about the effectiveness of the control mechanisms in place to prevent misuse and abuse. The EC also ignores the significant regulatory and economic disincentives for abusing and misusing hormone growth promoters. At the slaughterhouse, detention of carcasses, or a group of carcasses, causes disruption, ties up on-site storage pending residue testing results and is therefore avoided whenever possible by major processors. Product recall in Canada, or rejection of export shipments, incurs a significant financial loss. These real costs are in addition to the ever-present prospect of prosecution for applicable regulatory offences.

21. Sixth, the EC erroneously assumes that the problem with "black market" growth-promoting hormones in Europe is extended to Canada. Canada recognizes the concern of EC authorities on this issue, given the documented widespread use of such products in EC Member States and the reported involvement of organized crime.[11] Fortunately, Canada has not experienced the problems associated with the use of black-market drugs of the nature and extent experienced in Europe. The illegal use of any veterinary drug is a concern of authorities world wide, including in Canada. But use of illegal anabolic substances, whether for bodybuilding purposes or animal growth promotion, does not imply misuse of legal growth-promoting hormones. Reason suggests that if a safe legal product is available, calibrated for optimal performance at the specified dose, there is little incentive to engage in black-market drugs.

22. Seventh, by suggesting that the growth-promoting hormones in use in Canada are "sold freely 'over the counter'",[12] the EC implies that there is no veterinary supervision of these substances. This distorts the reality of the modern beef industry in North America. In Canada, only federally regulated meat-processing facilities are authorized to export meat products from Canada. These meat-processing facilities typically deal with large commercial feedlots. These feedlots in turn typically have in place animal health plans developed and implemented under the supervision of veterinarians and animal nutritionists. Thus, while a veterinarian generally does not directly supervise the

[11] Agence France Presse , June 3, 2002, "BELGIAN COURT FINDS FOUR MEN GUILTY IN "HORMONE MAFIA" MURDER TRIAL". The article reads in part: "A Belgian court has, according to this story, found four men guilty of the 1995 murder of a veterinary inspector who was probing a scam involving illegal animal hormones, according to a verdict made public late Monday. The story adds that the men are to be sentenced on Tuesday, almost two months after their trial began. The case of what became known as the "hormone mafia" caused an outcry in Belgium, after Karel Van Noppen was found shot dead in his white Mercedes in a lonely country lane in the northwestern city of Wechelderzande. Arms dealer Carl De Schutter, livestock dealer Germain Daenen, breeder Alex Vercauteren, and Albert Barrez, described as a travelling fair worker, were found guilty of the 1995 murder."

[12] EC Second Written Submission, at para. 108.

administration of the implants, animal health professionals are involved indirectly in the administration of growth-promoting hormones by way of developing animal health protocols. If the availability of "over the counter" drugs is of such a concern, the EC could restrict imports of meat products only from facilities that have in place animal-health management plans overseen by veterinarians.

23. In sum, the EC's purported assessment of the risks of misuse and abuse relies, not on available direct evidence from on-going random residue monitoring programs and realistic conditions of use, but on erroneous assumptions, invalid extrapolations and selective evidence. In conducting its purported assessment, the EC has failed to take into account process and production methods and relevant inspection and control measures, as required by Article 5.2 of the *SPS Agreement*. As such, the EC's purported risk assessment fails to properly evaluate the potential for adverse effects arising from misuse and abuse in Canada and as a consequence fails to satisfy the requirements of a risk assessment under Article 5.1 of the *SPS Agreement*.

Q5. In its comments on comments of the United States and Canada on experts replies to the Panel questions (in particular Question 13), the European Communities indicates that oestradiol 17β might be a "weak genotoxin" (para. 44). At what doses is genotoxicity observable *in vivo*? How are these doses comparable to those found in meat from cattle treated with growth promoting hormones? How would this assertion affect the identification of adverse effects and the evaluation of potential occurrence of these effects from consumption of meat from cattle treated with oestradiol 17β for growth promotion purposes?

24. The identification by the EC of oestradiol 17β as a "weak genotoxin" is a further indication of the questionable nature of the evidence on which the SCVPH based its conclusions. Based on the observation that the "magnitude of DNA adduct levels and mutagenic activities reported in these studies is not very high and seems to be much lower than encountered with most known genotoxins", the EC concludes that oestradiol 17β may be a "weak genotoxin". However, a more plausible conclusion, in light of the artificial test circumstances that produced these "weak" results,[13] is that oestradiol 17β is not genotoxic *in vivo* at any dose that is relevant to exposure to oestradiol 17β from meat from treated cattle.

25. In fact, none of Drs. Boobis, Boisseau and Guttenplan, the only three of the experts who are qualified to comment on issues related to genotoxic carcinogens, considered that there is evidence that oestradiol 17β is genotoxic *in vivo*. Even Dr. Guttenplan, who had some methodological disagreements with Dr. Boobis, ultimately concluded that "if you are talking about cancer, I don't think there is a risk from consumption below the ADI".[14]

26. Therefore, the studies relied upon by the EC to conclude that oestradiol 17β is a "weak genotoxin" do not support the conclusion that oestradiol 17β is genotoxic *in vivo.* These studies are therefore not relevant to the evaluation of the potential occurrence of adverse effects from exposure to oestradiol 17β from meat from treated animals.

[13] The reaction, for example, of Dr. Boobis to the test conditions underlying the EC's "evidence" is notable. In particular, he rejected the results reported in Exhibit EC-125, in which the doses needed to achieve a genotoxic effect were far, far in excess of any normal doses, and in fact ended in the death of a large number of the study animals.

[14] Due to the possibility of transcription inaccuracy, Dr. Guttenplan's exact wording may have differed slightly, but his meaning was clear.

Questions to the United States and Canada:

Q17. What legal procedures were used in your respective domestic legal systems to adopt the suspensions of obligations at issue? Would the same legal procedures apply to their abrogation?

27. The suspension of the obligations at issue was effected by Canada through the adoption of the *European Union Surtax Order*, the text of which was reproduced in Exhibit EC-4 (the *Order*). The *Order* was adopted on July 28, 1999 by the Governor General in Council (*i.e.*, the Governor General acting on the advice of Cabinet) and entered into force on August 1, 1999. The *Order* was based on statutory authority contained in subsection 53(2) and section 79 of the *Customs Tariff* and was adopted pursuant to authorization granted to Canada by the DSB on July 26, 1999. The termination of the suspension of obligations would be effected by an Order in Council revoking the earlier Order, *i.e.*, through an executive act.

Q18. Would you consider that, for the purpose of the DSU, Directive 2003/74/EC should be viewed as a new measure or as the continuation of the previous measure found to be inconsistent with the WTO Agreement, since it still imposes a ban?

28. Directive 2003/74/EC is a measure which purports to bring into compliance a previous measure (*i.e.*, Directive 96/22/EC) found to be inconsistent with the WTO Agreement. In doing so, it simply amends several provisions of the original non-compliant measure, all the while reaffirming the original ban and setting out new reasons (*i.e.*, the conclusions of the SCVPH opinions) that purport to justify that original ban. Therefore, since the main issue is whether the amendments brought by the new Directive rectified the inconsistencies of the old Directive, for the purposes of determining whether the EC has "removed" the inconsistencies, there is essentially only one measure that is continuing.

ANNEX C-4

REPLIES OF CANADA TO QUESTIONS POSED BY THE EUROPEAN COMMUNITIES AFTER THE SECOND SUBSTANTIVE MEETING

(18 October 2006)

EC Questions to United States and Canada:

Q1. Please explain, if possible in detail, what kind of scientific evidence on exposure-assessment from residues in meat treated with the six hormones for animal growth promotion was used by the United States and Canada when these substances were authorised? Was this exposure assessment a quantitative one? Please provide concrete reference to studies used in your exposure assessment and, if possible, to those of JECFA for the six hormones in question (in case you know the references).

1. The EC's repeated attempts to redirect the focus from its risk assessment to those of Canada and the United States are irrelevant and unhelpful in assisting the Panel in resolving this dispute. The pertinent issue in this case is whether the EC has complied with the recommendations and rulings of the DSB, including, *inter alia*, whether the EC's continued ban on imported meat from cattle that have been treated with growth-promoting hormones is based on a risk assessment, as required by Article 5.1 of the *SPS Agreement*. Thus, whether or not Canada has conducted an exposure assessment, quantitative or otherwise, is not legally relevant to the issues in this case. In any event, Canada's measures in regard to the hormones at issue are consistent with the international standards set by Codex.

2. In terms of the JECFA risk assessment, JECFA conducted detailed exposure assessments for each of the hormones at issue based on realistic conditions of use. The exposure assessments are contained in the Residue Monographs for each hormone published by JECFA. It is frankly quite surprising at this late stage in this dispute that the EC seems to be unaware of these detailed documents and of the detailed analysis in this regard undertaken by JECFA.

3. For the Panel's ease of reference, Canada provides the following table identifying the exposure assessments conducted by JECFA:

Substance	JECFA Document	Exhibit #
Oestradiol 17β	FNP 41/12	CDA-17
Progesterone	FNP 41/12	CDA-17
Testosterone	FNP 41/12	CDA-17
Zeranol	FNP 41/1	CDA-39
TBA	FNP 41/2	CDA-38
MGA	FNP 41/13 FNP 41/14 FNP 41/16	CDA-37 CDA-35 CDA-33

4. In terms of the exposure assessment for each natural hormone, the objective of JECFA's intake calculations was to "obtain conservative estimates of the theoretically possible excess dietary intakes of preferential eaters of meat that could be attributed to the approved uses of the products

reviewed".[1] If data for several time points after implantation were available, JECFA used the time points with the highest values to reflect the fact that no withdrawal period had been established for these products. Using JECFA's conservative food basket (300g muscle, 100g liver, 50g fat, and 50g kidney), the residue data were converted into human intake estimates, referred to as "Theoretical Maximum Daily Intakes" (TMDI). From the TMDI, JECFA subtracted estimated intakes of hormones from the untreated control population, in order to arrive at an "excess intake" value. This excess intake value was then compared with the ADI. In the case of each natural hormone, this conservatively inflated "excess intake" was only a fraction of the ADI: for oestradiol 17β, progesterone and testosterone, the figures are 2%-4%, 0.003% and 0.2%, respectively.[2] JECFA noted that "hormone concentrations found in individual populations of treated animals … were well within the physiological range of these substances in bovine animals. In addition, the calculated excess intakes contributed only a small additional hormonal burden to the background dietary intakes resulting from the consumption of other normal foods of both animal and plant origin".[3] On this basis and because of the wide margins of safety built into the analysis, JECFA concluded that "there would be no need to specify numerical MRLs for the three hormones".[4]

5. In terms of the exposure assessment for synthetic hormones, the procedure was more straightforward. JECFA calculated MRLs for each of the substances that ensured that consumption of meat products according to JECFA's conservative food basket would not lead to exposure in excess of the ADI. The residue depletion studies confirmed that residue levels in each of the target tissues would not exceed the recommended MRLs. In each case, however, JECFA used residue depletion studies based on realistic conditions of use, which is to say, according to the labelled instructions and good veterinary practice.

Q2. Please indicate, if possible in detail, whether your risk assessments, and if you know those of JECFA, of the six hormones in question for animal growth promotion have attempted to calculate the risk to humans from the additional exposure resulting from the residues in hormone-treated meat when used according to GVP and when GVP is not respected. Was it a quantitative exposure assessment? If so, please provide the precise reference to the data. (Please note that we are not referring here to residue-depletion studies contained in CAN Exhibit-17, since the EC has also conducted such residues depletion studies for its 1999-2002 risk assessments).

6. The answer to Question 1 also applies to this question. As is apparent from the answers above, in terms of the natural hormones, JECFA looked specifically at "excess intake", equivalent to what the EC refers to as "additional" exposure, of natural hormones from their use as growth promoters. The residue depletion studies set out in the Residue Monograph in Exhibit CDA-17 calculate levels of natural hormones in both treated and untreated control populations specifically to determine this "additional" exposure. Importantly, because the additional exposure is such a small fraction of the ADI, JECFA concluded that it was not necessary to set MRLs.

7. The EC appears to be claiming that the additional exposure to natural hormones when used as growth promoters creates risks. However, as the experts have explained, the EC simply fails to conduct exposure assessments to support this claim. Without an exposure assessment, it is not possible to conduct a risk characterization to determine whether the additional exposure at issue would be sufficient to push total exposure to natural hormones from all dietary sources over the ADI.

[1] JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12, at p. 83 (Exhibit CDA-17).
[2] *Ibid.*
[3] *Ibid.*, at pp. 83-84.
[4] *Ibid.*, at p. 84.

8. With reference to the EC's claim that it has conducted residue depletion studies, the only such studies that the EC has conducted for its 1999-2002 opinions appear to involve contrived misuse scenarios for the synthetic hormones that do not reflect realistic conditions of use (*e.g.*, Exhibits EC-11 and EC-17). In any event, as Dr. Boobis has explained in detail in his response to Panel Question 62, several studies show that even with unrealistic misuse scenarios (*e.g.*, 10-fold increases in dose) exposure would only barely exceed recommended MRLs. It is hardly surprising that MRLs may be exceeded if one pumps an animal full of veterinary drugs in doses that well exceed the recommended level. That they may be exceeded, however, says nothing about the occurrence or frequency of overdosing under realistic conditions of use.

Q3. The EC understands that some of the experts (Drs. Guttenplan, Sippel and Cogliano) have stated that it is not possible to determine with accuracy the dose-response curve at the very low levels of exposure from these hormones in general and when used for animal growth promotion. Do you agree with these statements? If not, could you please provide the precise references to scientific studies where this has been done? What would be the implications of this impossibility for the need to perform a quantitative or qualitative exposure assessment for these hormones when used for animal growth promotion?

9. In indicating that it is not possible to determine with accuracy the dose-response curve at very low doses, these three experts were referring to the difficulties inherent generally in linear modelling of dose-response curves far below the lowest experimental doses. Those experts, such as Drs. Boobis and Boisseau, who reviewed the specific toxicological evidence related to actual adverse effects from oestradiol 17β, as opposed to modelled effects, concluded that oestradiol 17β is not genotoxic *in vivo*. They were categorical about this in both their written answers and their advice to the Panel. Even Dr. Guttenplan, who appeared to have some methodological disagreements with his colleagues, ultimately responded that "if you are talking about cancer, I don't think there is a risk from consumption below the ADI".[5] Therefore, since these experts confirm that there is a dose below which adverse effects do not occur (as a result of the identification of NOAELs), there is no need to use the uncertain modelling techniques referred to by the three experts mentioned in the question.

10. In any event, Drs. Sippell and Cogliano are not qualified to comment on the evidence of thresholds for potential carcinogenic potential of oestradiol 17β at low doses. This is not their field of expertise. While they may have professional opinions on the weaknesses of linear dose-response modelling techniques in determining the shape of the dose-response curve at low doses, these opinions must yield to the expert advice of those who are qualified to evaluate actual carcinogenic potential at low doses. In other words, the specific advice of Drs. Boobis, Boisseau and Guttenplan is the relevant advice for assessing the risks from low-dose exposures to oestradiol 17β from meat from treated animals.

Q4. If you were to agree that scientists cannot define the dose-response curve as explained in the previous question, would this state of scientific knowledge be defined as "scientific uncertainty" in this area? If not, please explain.

11. The issue is not whether the advice of the experts revealed the existence of "scientific uncertainty" or "vivid debate" on certain issues. Rather, the issue is whether there is "scientific uncertainty" about the specific issues that are relevant to this dispute. As described in the answer to the question above, uncertainty or debate between the experts about the limitations in techniques for modelling the shape of the dose-response curve is not relevant in light of the unanimity expressed by the most qualified experts that there are doses of exposure to oestradiol 17β below which cancer does not result. In other words, since the qualified experts have identified that there are thresholds below

[5] Due to the possibility of transcription inaccuracy, Dr. Guttenplan's exact wording may have differed slightly, but his meaning was clear.

which adverse effects will not occur (as a result of the identification of NOAELs), there is no need to engage in uncertain linear modelling of the dose-response curve. As such, any uncertainty that may persist when such modelling is employed is not relevant to the evaluation of carcinogenic potential of oestradiol 17β at low doses from meat from treated animals.

12. It is therefore not sufficient to point to general disagreement between the experts on any issue and claim that there is scientific uncertainty such that a minority scientific opinion exists. It is necessary to look at the nature and relevance of the issue of purported uncertainty, the relevance of the respective qualifications of the participants in the debate, and the nature of the evidence relied upon by each participant to support their respective interpretation. In this case, the opinions of the generalists (Drs. Sippell and Cogliano) as to uncertainty inherent when modelling techniques are employed are not relevant in light of the expert advice of the cancer specialists (Drs. Boobis, Boisseau and Guttenplan) that the carcinogenic potential of oestradiol 17β exhibits a threshold below which it will not occur.

Q5. Could you please explain what is your position on the existence or non existence of an international standard for MGA for the purposes of Articles 2, 3 and 5 of the SPS Agreement in these disputes?

13. As a result of opposition by the EC in Codex, that organization has not yet adopted as an international standard the revised recommendations by JECFA for MRLs for MGA. There is therefore currently no international standard for the purposes of Article 3 of the *SPS Agreement*. However, JECFA has conducted a risk assessment of MGA and has allocated an ADI. This means that it has concluded that there are "no appreciable risks" to human health from exposure to residues of this hormone from meat from treated animals. Other agencies and health authorities have conducted similar assessments and have come to the same conclusion. Therefore, the EC's divergent conclusion that there is insufficient evidence to conduct a risk assessment of MGA is not justified, such that its provisional ban on MGA is not justified by Article 5.7 of the *SPS Agreement*. As a result, the EC has also failed to base its ban on MGA on a risk assessment appropriate to the circumstances, contrary to Article 5.1 of the *SPS Agreement*.

EC Questions to Canada:

Q1. In relation to your example for the oestrogen level in pregnant women (para. 53 of your Oral Statement) could you please comment on Exhibit EC-56 where there is evidence that *in utero* exposure to oestradiol has given rise to a number of abnormalities and suspected of an increased rate of cancer? Assuming that this finding is related to the low-dose response uncertainty, do you have any evidence that the 2ng added to endogenous oestrogens production are not likely to have any such effect?

14. The EC misstates the conclusion of the study in Exhibit EC-56, which was Study 13 (Kaijser *et al.*, 2001). That study does not provide "evidence that *in utero* exposure to oestradiol has given rise to a number of abnormalities and suspected of an increased of cancer", as claimed by the EC.

15. The study set out to explore the hypothesis that the risk of breast cancer is influenced by hormonal exposure *in utero* by comparing breast cancer rates in twins. However, the study does not conclude that exposure to oestradiol gives rise to a number of abnormalities and an increased risk of cancer. In fact, the study concludes that for female co-twins with male co-twins, a high birth weight constitutes a strong independent risk factor for breast cancer. The same relationship between high birth weight, which is often seen as a proxy for oestrogen exposure, and risk of breast cancer was not seen in female twins with female co-twins. The authors speculated that the presence of androgens produced by the male co-twin, not oestrogens, may help explain the increased risk. It is a stretch of

Herculean proportion to conclude, as the EC does, that this study is evidence that *in utero* exposure to oestrogen causes an increase in cancer.

16. In any event, as Dr. Boobis states in his answer to Panel Question 62, "given that exposure to oestradiol from meat of treated animals would be extremely low, particularly relative to endogenous hormone levels, which increase during pregnancy, (e.g. see *Weiss, 2000*) the findings of the Kaijser et al study provide no evidence for risk from exposure to oestradiol residues in meat from treated animals".

17. The second part of the EC's question is premised on a nonsensical theory of low-dose exposure. Pregnant women produce daily in the range of 37,000,000 ng of oestradiol, much of this produced in the placenta adjacent to the developing fetus. As Dr. Boobis noted, exogenous natural hormones are indistinguishable from their endogenous counterparts once absorbed into the human system. Thus, the 2 ng of bioavailable oestradiol from meat is quickly integrated into the circulating levels of endogenously produced oestradiol. As a result of the homeostatic control mechanism, endogenous production is adjusted to take into account exogenous exposure. Thus, the low dose of exogenous oestradiol to the mother does not translate into a low dose to the fetus. Moreover, even if the background circulating levels were increased by 2 ng, it is absurd to claim that the fetus is exposed to a "low dose", given its pre-existing exposure to substantially greater amounts of oestradiol endogenously produced by the mother.

18. One is comforted in concluding that the EC's speculative propositions in this regard have no scientific justification as, to Canada's knowledge, no European health authority is advising pregnant women to avoid consumption of foods containing oestrogens out of concern for potential adverse effects on the fetus. If the EC truly believed that the negligible amount of oestrogens from dietary sources was a risk factor for reproductive cancers in the fetus, then one would expect responsible EC health authorities to act to protect, or at the very least advise, the unsuspecting public. Tellingly, they have not done so.

Q2. As regards the reference to Carbadox (see para. 67 of CDA's oral statement of 3 October): Could you please explain briefly what happened and what were the reasons for which you have changed your risk assessment for Carbadox? Was it simply on the ground that Carbadox was found to be genotoxic or was it because you have carried out before a quantitative or qualitative exposure assessment for the residues in pork meat treated with Carbadox?

19. The reference to *carbadox* in paragraph 67 of Canada's Oral Statement on 3 October 2006 is simply to illustrate a point raised by the JECFA representative during the session with the Panel's expert advisors. Codex provides a mechanism whereby its Members can bring new information to the attention of the responsible bodies and request a re-evaluation of existing standards, recommendations or guidelines. Indeed, this mechanism is routinely used by Codex members. As many countries base their domestic SPS measures on Codex standards, recommendations and guidelines, as required by Article 3.1 of the *SPS Agreement*, one would expect that, if a Member of Codex had new, pertinent information that it claims casts doubt on the validity of an existing Codex standard, it would, as a responsible member of Codex, avail itself of the re-evaluation procedure in order to protect not just its own citizens but those of other countries that rely on such standards. Tellingly, in this case, the EC has failed to do so.

20. As to the history of the re-evaluation of *carbadox*, at the Thirteenth Session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) *ad hoc* working group on priorities, Canada requested a re-evaluation of *carbadox* on the basis of new information, including analytical information showing the presence of the metabolite *desoxycarbadox* in the tissues of pigs. Japan and Thailand also made similar requests in relation to other veterinary drugs (*e.g.*, flumequine). The

Working Group recommended that these veterinary drugs be re-evaluated and forwarded these recommendations to the CCRVDF.[6]

[6] CCRVDF, Report of the *Ad Hoc* Working Group on Priorities, 4-7 December 2001, Thirteenth Session, Agenda Item 13, CRD 2, at para. 4.

ANNEX C-5

COMMENTS BY CANADA ON THE REPLIES OF THE EUROPEAN COMMUNITIES TO QUESTIONS POSED BY THE PANEL AFTER THE SECOND SUBSTANTIVE MEETING

(31 October 2006)

INTRODUCTION

1. In this document Canada provides comments on the EC's answers to questions 1, 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14 and 15 from the Panel after the Second Substantive Meeting, as filed on 18 October 2006.

Q1. With reference to the statement by the European Communities, *inter alia* in para. 12 of the EC reply to Question 3 of the United States, do the parties consider that a Panel is entitled to address "systemic claims" or issues related to "systemic obligations" and, if so, to what extent?

2. In its response to this question, the EC characterizes its "systemic claims" as being "procedural in nature" and "independent of substantive obligations". This reasoning reflects the fundamental flaw that has driven the EC's actions in this dispute from the beginning, and it is simply not supported by the text of the *DSU*. The DSB authorization of Canada's suspension of concessions is based on findings of breaches by the EC of its "substantive obligations". That authorization, and any measures taken pursuant to it, cannot therefore be rendered without effect simply through "procedural" manoeuvring that is independent of an assessment of the underlying "substantive obligations". The EC challenges Canada with claims that are "procedural in nature" precisely to avoid having to demonstrate its compliance with its substantive obligations. However, the only way for the DSB authorization no longer to have effect is for the EC to confirm compliance with its substantive WTO obligations (*i.e.*, by succeeding on its "direct claims").

Q2. With reference to the US rebuttal, para. 27, do the parties consider that a measure that does not comply with the requirements of Article 5.7 SPS would automatically be in breach of Article 2.2 SPS, or Article 5.1 SPS, or both?

3. Canada has no comment on the EC's response to Question 2, other than to note that Canada has addressed in paragraphs 113 to 119 in Canada's Second Written Submission the EC's argument that Article 5.7 creates a "special regime".

Q3. When and how was each of the following documents made available to Canada and the United States? Please answer independently for each of the documents mentioned below:

- **(i) 1999 Opinion;**
- **(ii) 2000 Opinion;**
- **(iii) 2002 Opinion;**
- **(iv) each of the "17 studies".**

4. In discussing those of the 17 studies that the EC failed to disclose to the defending parties, the EC refers to one study that "was from the start not meant for publication (Exhibit EC-7), as it contained the samples of meat collected from the US supermarkets that was sent for analysis in the

European laboratories".[1] However, Exhibit EC-7 appears to relate to Commission Study 1 and involved a comparison of assay methods for detecting hormone residues in meat, not analyses of meat samples collected from US supermarkets. The study of meat samples from US supermarkets appears to be one of the studies conducted by Professor Rainer Stephany for the Community Reference Laboratory in Bilthoven, The Netherlands, under the rubric of Commission Study 6. The EC has not disclosed the results of this study, but submitted instead an article by Dr. Stephany for an NGO newsletter (Exhibit EC-19).[2] Dr. Stephany appears to have issued three interim reports analyzing various samples of meat and meat products from the United States:

- The first interim report is entitled "Results of 'hormone' residue analyses of bovine meat and liver imported into the EU and originating from the USA 'Hormone Free Cattle Program' ", First Interim Report;[3]

- The second interim report is entitled "Results of 'hormone' residue analyses of bovine meat and liver originating from the USA domestic market", Second Interim Report;[4] and

- The third interim report is entitled "Results of 'hormone' residue analyses of bovine liver originating from the USA and imported into the EU as petfood", Third Interim Report.[5]

5. What is remarkable is that of the three interim reports authored by Dr. Stephany specifically analyzing samples of meat and meat products from the United States, only the results of the third report have been submitted to the Panel. This study, Exhibit EC-53, relied upon by the EC in response to Panel Question 4, relates to petfood.[6] Those studies that specifically measured the level of hormone residues in meat samples for human consumption appear to have been withheld by the EC on the basis that "they were not meant for publication". Furthermore, in what is clearly an error, the EC refers to Exhibit EC-53 (petfood!) to buttress its argument that it has assessed the level of risk from meat sold in US supermarkets.

6. The disclosure of petfood results while withholding actual human food results is particularly troubling given the EC's assurances that it conducted an "exposure" assessment. But what better evidence to assess exposure than results from samples of actual human food. Ignoring this evidence, the EC instead relies on hypothetical scenarios of misuse in an attempt to demonstrate likelihood of risk. Moreover, not only did the EC fail to take data from actual human exposure into consideration in assessing exposure, it withheld these data from the Panel and the defending parties. It cannot be excluded that the data assembled by Dr. Stephany did not support the EC's absurd conclusions concerning the extent of misuse and abuse in Canada and the United States. Indeed, it is entirely plausible that these data confirm the results of Canada's Codex-consistent national residue monitoring program, results which the EC has also ignored. Thus, the failure to take into consideration actual data

[1] EC's Responses to Questions to the Parties from the Panel in Connection with the Second Substantive Meeting (EC's Responses after the Second Meeting), at para. 11.

[2] Also see Rainer W. Stephany, "Hormones in meat: different approaches in the EU and in the USA" (Exhibit EC-49, also Exhibit CDA-12).

[3] See Canada's Responses to Questions to the Parties from the Panel in Connection with the Second Substantive Meeting, Canada's response to Panel Question 3, fn 2. Also see Exhibit EC-49 (also Exhibit CDA-12), ref. no. 25. The existence of the first report is confirmed by references to it in the 1999 SCVPH Opinion, at pp. 31 and 117 (Exhibit CDA-2), and the Draft Assessment of Risks of Abusive Use, fn. 24 (Exhibit EC-73).

[4] See Exhibit EC-49 (also Exhibit CDA-12), ref. no. 26.

[5] R.W. Stephany and F. André, "Results of "hormone" residue analyses of bovine liver originating from the USA and imported into the EU as petfood, Final Report" (Exhibit EC-53).

[6] EC's Responses after the Second Meeting, at para. 15.

from meat samples taken in US supermarkets implies that the EC has been selective and self-serving in the data that it considered. Given the EC's underlying theme that it lacks modern residue data, it is all the more surprising that the EC buries these data under the proviso that they were "from the start not meant for publication".

Q4. Has the European Communities assessed in a systematic manner the existence and level of risks from failure to observe good veterinary practices with respect to the administration of oestradiol 17β as a growth promoting hormone to cattle, in particular in the United States' and Canada's markets? If so, please indicate where this assessment is to be found in the evidence provided to the Panel.

7. Canada has several specific points to make in relation to the EC's response to Panel Question 4. As a general comment, however, the EC persists in its practice of referring to exhibits to support its claims in the apparent hope that nobody will read the exhibits. A close review of these exhibits indicates that, in many cases, they simply do not support the EC's position. Accordingly, the Panel would be well-advised to scrutinize closely the EC's putative supporting evidence.

8. First, in paragraph 14, the EC refers to a number of exhibits that identify a potential hazard. Not surprisingly, if one administers a veterinary drug in amounts well in excess of approved doses (*e.g.*, 10-fold) it is plausible, although not necessarily so,[7] that residues of that drug could exceed recommended MRLs. Thus, many of the articles cited by the EC are hardly groundbreaking science. Although the EC identifies a potential hazard, the EC's exhibits say nothing about the frequency with which their concocted, experimental scenarios would occur under realistic conditions of use. Without an assessment of frequency, the EC's analysis cannot be said to evaluate the likelihood of adverse effects occurring, as required for a risk assessment consistent with Article 5.1 of the *SPS Agreement*. The defectiveness of the EC's approach is perhaps best illustrated by an analogy. It is possible that in European abattoirs contaminants, such as animal feces, could enter the human food system. Animal feces potentially carry numerous bacteria, which are potentially hazardous to human health. Thus, having identified a human health hazard, would it be acceptable for a WTO Member to ban European meat on the basis that feces could potentially enter the human food chain, without doing any analysis of the frequency with which animal feces actually enter the system? Canada thinks not. By extension, it is not acceptable merely to identify potential health hazards from the abusive use of hormones without any analysis of the frequency of such misuse under realistic conditions of use.

9. Second, contrary to the EC's claim in paragraph 14, none of the Experts confirmed that "if GVP is not observed the ADIs and the MRLs proposed by Codex become useless." The EC would be well-advised to familiarize itself with the role of MRLs in its own residue-monitoring program.[8] Quite simply, ADIs and MRLs are not "useless" if GVP is not observed. MRLs provide a means for detecting whether, as a result of the failure to follow GVP or some other reason, residues exceed acceptable limits such that ADIs are likely to be exceeded.[9] As with any veterinary drug (or pesticide, for that matter), MRLs provide a mechanism for detecting potential abuse (over-use, failure to follow withdrawal periods, *etc*.). For all the EC's talk of misuse and abuse in Canada and the United States, it puts forth no data that attempt to quantify the frequency with which residues in Canada actually

[7] See Dr. Boobis' review of Exhibit EC-17 (study 5) (Iris G. Lange, A. Daxenberger & H.H.D. Meyer, "Hormone contents in peripheral tissue after correct and off-label use of growth promoting hormones in cattle: Effect of the implant preparations Finaplix-H®, Ralgro®, Synovex-H® and Synovex Plus®") where he quotes the authors of the study as concluding "[t]reatment with zeranol and testosterone propionate, even after multiple application does not cause any problems, as far as infringement of threshold levels is concerned", Panel Questions to the Experts, Dr. Boobis' response to Question 62, at p. 50.

[8] Questions and Answers on Residues and Contaminants in Foodstuffs, Brussels, February 19, 2003, online at: http://ec.europa.eu/food/food/chemicalsafety/residues/fcr_qanda_en.pdf.

[9] See Panel Questions to the Experts, Dr. Boobis' response to Question 46, at pp. 41-42.

exceed recommended MRLs. And because it has no evidence, it attempts to discredit the universally accepted concepts of ADI and MRL.

10. Third, in terms of the EC's evaluation of the level of risk from imports coming from Canada and the United States, the EC cites its obviously self-serving "draft" "working document", filed as Exhibit EC-73.[10] The EC claims that this document takes into account "specific, real and undisputed instances of abuse and/or misuse".[11] This is simply a further attempt by the EC to use distortions, inappropriate extrapolations and unfounded assumptions to undermine Canadian control practices. Canada has addressed in its answer to Panel Question 4 the major flaws in the EC's putative risk assessment.

11. Fourth, as Canada indicated in its comments on Question 3, the EC cites Exhibit EC-53, a review of petfood samples, as support for its assertion that meat sold in US supermarkets was assessed. Curiously, rather than data from human food samples (which the SCVPH failed to consider and the EC has withheld from this Panel), the EC cites petfood data. Although the relevance of residues from hormonal treatment of cattle found in liver destined for use in petfood to food destined for human consumption is debatable, the petfood data do not support the EC's conclusions regarding misuse and abuse of growth-promoting hormones in Canada or the United States:

- first, it is not surprising that residues would be found in some livers, as tissues destined for manufacture of pet food may be from animals considered unfit for human consumption;

- second, despite this, none of the residue results reported (Annex 5 of the report) exceeded the Codex MRLs for trenbolone in cattle liver or the MRLs recommended by JECFA for MGA in cattle liver. In addition, no confirmed residues of zeranol or its metabolites were found in any samples (thus, even in animals unfit for human consumption, there is no evidence of zeranol use, let alone misuse);[12]

- third, the two analytical laboratories also reported analytical results for oestradiol, progesterone and testosterone but stated that there was no basis for classifying the results in terms of "normal" or "abnormal". Since the EC cannot distinguish between "normal" and "abnormal" levels of these compounds, one must wonder on what basis their so-called "additional risk" can be associated with the consumption of meat from treated animals produced in North America; and

- fourth, no evidence of use of "black market" or unauthorized hormones was found in these samples.

Q5. In its comments on comments of the United States and Canada on experts replies to the Panel questions (in particular Question 13), the European Communities indicates that oestradiol 17β might be a "weak genotoxin" (para. 44). At what doses is genotoxicity observable in vivo? How are these doses comparable to those found in meat from cattle treated with growth promoting hormones? How would this assertion affect the identification of adverse effects and the evaluation of potential occurrence of these effects from consumption of meat from cattle treated with oestradiol 17β for growth promotion purposes?

[10] European Commission, Assessment of Risks of hormonal growth promoters in cattle with respect to risks arising from abusive use and difficulties of control, Draft Report by special working group of external private experts and European Commission officials, Brussels, April 29, 1999.

[11] EC's Responses after the Second Meeting, at para. 15 (emphasis omitted).

[12] R.W. Stephany & F. André, "Results of "hormone" residue analyses of bovine liver originating from the USA and imported into the EU as petfood, Final Report", at pp. 28-31 (Exhibit EC-53).

12. The first thing to note about the EC's response to this question is that the EC has very conveniently stopped referring to oestradiol 17β as "genotoxic" and has begun referring to it as "mutagenic". This is perhaps not surprising in light of the advice of experts such as Dr. Boobis that "not all genotoxicity is necessarily mutagenic".[13] The EC has realized that even establishing oestradiol 17β as genotoxic is insufficient to demonstrate adverse effects; it must also establish it is mutagenic, so it has switched the terms it uses in its responses. The reality is, however, that the Experts advised that there is no evidence of *in vivo* genotoxicity of oestradiol 17β, let alone evidence of mutagenicity, which would be required for oestradiol 17β to be considered carcinogenic through a mode of action other than its hormonal activity.

13. The lengths to which the EC goes to defend its reliance on Exhibit EC-125 are also quite remarkable. Responding to criticism that the dose used in the study was too high to be relevant to conclusions about genotoxicity under realistic conditions, the EC asserts that negative conclusions should not be drawn from the "very high" dose because the precise dose is not known as the study did not determine it. Undaunted by the absence of this information, the EC simply makes it up. Based on "assumptions" and "estimates", the EC derives a figure for the rats' daily exposure to oestradiol 17β, and then suggests that the dose used in the study was not unreasonable after all. However, applying the calculations made by the United States in its answers to this question, even the EC's "estimated" daily exposure of 200 micrograms/kg/bw is still 8,000 greater than that from meat from treated animals.

14. Moreover, in its efforts to portray the test conditions in that study in the most favourable light possible, the EC overlooks one critical piece of information: a large number of the animals in the study died from the dose administered. In other words, no amount of recalculation based on assumptions and estimates can alter the fact that the dose actually administered in the study was so great as to overwhelm the normal bodily functions such that the animals died before any genetic effects could be observed. Whatever notional number the EC places on the daily dose in that study, it is not comparable to the dose received from meat from treated animals, such that the results of that study would be relevant to exposure to meat from treated animals.

15. The EC then quite confusingly, in paragraphs 19 and 20, relates the results of the rat studies to estimates of daily production rates in pre-pubertal children. By arguing that the rat study demonstrates that oestradiol 17β has "mutagenic effect" at a dose "within the 1000 safety margin", the EC appears to be making a significant change to its interpretation of the evidence. The SCVPH concluded that oestradiol 17β was "genotoxic" and that there is no threshold below which this genotoxic effect would not occur. The EC now seems to be saying that there is a threshold for "mutagenic effects", but that this threshold is within the safety margins implicit in the JECFA ADI. Since this new conclusion is based on a combination of two very different sets of data (*i.e.*, the EC's own estimates of the daily dose in the rat study and the Klein estimates of daily production), neither of which has been proven to be valid, the EC's arguments have strayed so far from actual scientific evidence to barely warrant comment.

16. In any event, the SCVPH declined to conduct a dose-response assessment as a result of its conclusion that oestradiol 17β is genotoxic and does not exhibit a threshold. Therefore, even if the EC's interpretation of Exhibit EC-125 were correct – and it is not – it would amount to nothing short of a concession by the EC that a dose-response assessment should have been conducted by the SCVPH in order to determine the threshold of mutagenicity.

[13] See Panel Questions to the Experts, Dr. Boobis' response to Question 2, at p. 9, as well as Dr. Boobis' advice during the meeting with the Experts.

17. Finally, the EC claims that the "dose administered is not very critical for *in vivo* genotoxicity", but this precise claim has been directly countered by Dr. Boobis, the most qualified of the Experts to advise on this point.[14] He advised that understanding the mode of action of the potential genotoxicity of a substance is critical in understanding whether there will be a threshold. The observation of genotoxicity at very high doses is not conclusive of whether oestradiol 17β can be considered genotoxic *in vivo*. In fact, the failure to observe the same genotoxic effect at low doses confirms that the mode of action is such that a threshold is present.

Q6. Should the Panel agree with the European Communities' main claim that the United States and Canada have breached Article 23 of DSU read together with Articles 21.5 and 22.8, what would be the consequences of such a conclusion for the United States and Canada? More particularly, would the United States and Canada:

(a) be expected to withdraw the suspensions of concessions or other obligations or suspend their application?

(b) be expected to initiate an Article 21.5 procedure against the EC? or

(c) would they be expected to do both?

(Please note that the Panel is fully aware of its obligations under Article 19 DSU)

18. There is no merit to the EC's claims that provisions of the *DSU* acquire a different meaning when "read together" with other provisions than they would have when read on their own. Article 23 read in conjunction with either of Article 22.8 or 21.5 cannot create obligations for Canada that it does not have under Article 23 on its own. The issue, therefore, is not what additional obligations under the *DSU* these three provisions together create for Canada to act, but what Canada's obligations are under the *DSU*. On that point, if the Panel were to accept the EC's claims on *DSU* grounds alone, the EC's response that the Panel should find that Canada must both cease its suspension of concessions and initiate compliance proceedings under Article 21.5 is also totally without merit. If the Panel were to accept a claim under the *DSU*, only one of the two options, and not both, can be a consequence.

19. On the one hand, if the Panel should find, simply on the basis of the EC's *DSU* claims, that Canada has an obligation to withdraw its suspension of concessions, there cannot be findings of an obligation to initiate, at the same time, Article 21.5 proceedings. To require both would be tantamount to turning Article 21.5 into a positive obligation always to initiate compliance proceedings in the event of a disagreement. This is not the intent of that provision. On the other hand, a finding by the Panel that Canada had an obligation to initiate Article 21.5 proceedings only makes sense if the Panel finds simultaneously that the suspension of concessions may remain in force until the dispute is resolved.

Q8. The Panel understands that the European Communities initiated risk assessments with respect to all six hormones at issue (see, e.g., Directive 2003/74/EC, third introductory paragraph).

(a) Could the European Communities confirm, with respect to oestradiol 17β and in light of its statement in para. 192 of its rebuttal and its comments on Question 14 of the Panel to the experts, whether:

[14] *Ibid*., Dr. Boobis' responses to Question 16, at p. 19, and Question 19, at p. 22, as well as Dr. Boobis' advice during the meeting with the Experts.

(i) it proceeded through the four steps of risk assessment identified by Codex; or

(ii) could have proceeded through the four steps but decided not to do so in light of its findings on genotoxicity of oestradiol 17β?

(b) Could the European Communities confirm, with respect to each of the other five hormones at issue, at what stage(s) of its risk assessment it considered that relevant scientific evidence was insufficient and decided to provisionally ban the importation of meat treated with those hormones on the basis of available pertinent information.

20. In its response to Question 8, the EC again claims that the SCVPH has conducted all four steps of a risk assessment and then claims, in paragraph 35, that Canada's main objection is that the SCVPH has not conducted an exposure assessment (the third step). Both of these claims are wrong.

21. With respect to the four steps of the risk assessment, Canada's main claim is that the SCVPH did not properly complete the second step of the risk assessment, the hazard characterization, as a result of its scientifically unjustified interpretation of the evidence related to genotoxicity and the potential for endocrine disruption. Based in particular on its unsupported conclusions about genotoxicity, the SCVPH declined to conduct a dose-response assessment (which is part of the hazard characterization) of oestradiol 17β. It also failed to assess the dose at which there are risks of endocrine disruption, particularly among pre-pubertal children. The Experts confirmed these failures.

22. With respect to the EC's purported exposure assessment, the EC seems also to have confused what in fact constitutes an exposure assessment. The EC's claims to the contrary, the SCVPH's assessment in section 4.1.5 of its 1999 Opinion does not amount to a complete "exposure assessment". At best, that section draws conclusions (incorrect, as Canada has explained elsewhere) about relative exposure (*i.e.*, the ratio of exogenous exposure to endogenous production). It provides little information on the overall exposure to hormones from exogenous sources, and it provides no assessment whatsoever on the implications of a change in the understanding of this ratio (even were it to be confirmed, which it has not) for the identification of adverse effects on pre-pubertal children. It certainly does not, as suggested by the EC, call into question the ADI set by JECFA, as that ADI is not based on a calculation of endogenous production in population sub-groups. Rather, the SCVPH simply asserts, without evidence or justification, that new data regarding exposure levels relative to endogenous levels reveal new risks.

23. Moreover, even if this section were to be considered an exposure assessment, the calculations contain several problems. First, the SCVPH assumes an "acceptable daily intake" of 102 ng/person/day. This value was derived from US Food and Drug Administration tolerances for permitted incremental increases of oestradiol over and above the concentrations naturally present in untreated animals. However, this value does not represent the actual amounts of estradiol found in edible tissues and so does not represent an estimated amount to which consumers will be exposed. A more accurate (yet still very conservative) estimate of excess daily intake of total estrogens from eating beef from treated animals is 30-50 ng/person/day (*i.e.*, one-third to one-half of the EC's erroneous estimate). This figure is based on actual residue depletion data assessed by JECFA.[15]

24. Second, the SCVPH based its calculation on the results of the Klein assay, which indicated that blood levels of estradiol in prepubertal boys were 100-fold lower than previously reported. Canada has demonstrated the flaws of the Klein assay on several occasions and the validity of this

[15] JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12, at p. 83 (Exhibit CDA-17).

assay was discussed in detail at the meeting with the Experts. While there seemed to be general agreement among the Experts that blood levels of estradiol in prepubertal children may be lower than previously believed, there was no consensus reached on the magnitude of the difference, and none of the Experts provided convincing scientific evidence in support of the 100-fold difference cited by the EC. The EC has itself recognized the inaccuracy of the Klein assay results.[16]

25. Third, the EC speculates that the metabolic clearance rate of estradiol in children is one-half that of adults. No scientific data have been presented to support this speculation. As a result of numerous methodological and calculation errors, the portion of the SCVPH opinion that the EC claims constitutes the "exposure assessment" simply does not satisfy what is required of an exposure assessment.

26. The SCVPH's failure to complete a hazard characterization or proper exposure assessment in the end prevented it from completing a proper risk characterization. The EC defends the SCVPH's risk characterization as "qualitative", but this simply amounts to an acknowledgement that the SCVPH did not have the information it needed to characterize the risk, because it did not attempt to produce that information.

Q9. Can the European Communities explain the meaning it gives to the term "mere doubt" in para. 181 of the EC second submission (US case)?

27. In paragraph 181 of its rebuttal submission (U.S. case), the EC stated that "[u]nder Article 5.7 a mere doubt must be sufficient", suggesting that mere doubt about the sufficiency of scientific evidence would satisfy the first requirement of Article 5.7. In its answers to Panel Question 9, the EC backtracks from this untenable position and suggests that the doubts must be "reasonably serious", as would be the case where the pertinent available evidence is "contradictory, inconclusive or incomplete." The EC appears to suggest that where the pertinent information is "contradictory, inconclusive or incomplete", the relevant scientific evidence will be insufficient to perform a risk assessment.

28. Several points should be emphasized. First, new evidence must be assessed in the light of all relevant evidence, including the pre-existing evidence. As Dr. Boobis indicated during the meeting with the Experts, all evidence is not of equal probative value and a weight-of-evidence approach is necessary to determine the comparative weight to be given to particular data in the light of the total available evidence. Second, the new evidence must lead to the conclusion that the totality of relevant scientific evidence is insufficient to perform a risk assessment. This is a question of fact. Third, contrary to the EC's suggestion, the determination of whether a WTO Member has acted consistently with the requirements of Article 5.7, including the determination of whether the evidence is insufficient to perform a risk assessment, is a question to be determined objectively by the Panel, not subjectively by a Member, "depending on the Member's chosen level of protection", as the EC puts it.[17] Fourth, in the specific circumstances of this case, no Expert advised that the so-called "new" evidence adduced by the EC demonstrates that important gaps, insufficiencies or contradictions in the relevant scientific evidence exist such that a risk assessment could not be performed. Indeed, in terms of the five provisionally banned growth promoters, several Experts specifically advised that the new

[16] See EC Comments on the Replies by the Panel Experts, Question 38.

[17] See Canada Oral Statement, October 2 and 3, 2006, at para. 66. Canada refers the Panel to the unadopted panel report in *European Communities – Measures Affecting the Approval and Marketing of Biotech Products*, at paras. 7.3233-7.3246. That panel dismissed similar arguments advanced by the EC that the appropriate level of protection influences the determination of "insufficiency" of evidence.

data do not demonstrate any important gaps, insufficiencies or contradictions in the relevant scientific evidence.[18]

29. In relation to carbadox, cited by the EC in paragraph 44, the EC makes the rather obvious point that sometimes the re-evaluation of substances on the basis of new information may lead to different conclusions. The fact that JECFA revised its conclusions concerning carbadox after a request to re-evaluate this substance by a Codex Member (Canada) illustrates how the system should function and says nothing about whether, in respect of the substances at issue before the panel, new information casts doubt on the previous conclusions. As discussed above, clearly it does not.

Q11. What is meant by no "additive risk"? Please explain to which "risks" these are "additive".

30. In its response to this question, the EC repeats the erroneous and unsupported assumptions and claims that have from the beginning plagued its approach to the regulation of these hormones. It claims that there is a risk of cancer from normal background levels of hormones, that exposure to exogenous sources automatically increases these background levels, and that this increase in the background levels automatically alters the existing risk. These claims constitute a serious misrepresentation of the scientific evidence.

31. First, the EC has submitted no evidence that "life-time exposure of humans to the levels of endogenous production of oestrogen … are sufficient to cause and/or promote cancer in some individuals", despite its claim that this is "scientifically not disputed".[19] To the extent that the EC is suggesting that exposure to hormones has a cumulative effect, that background levels alone have adverse effects and that hormones initiate cancer, these assertions are all simply wrong. The only conclusion that is not scientifically disputed is that hormones can promote cancer growth, but they do so through receptor-mediated modes of action that exhibit a threshold below which it does not occur. The evidence of this effect comes from studies involving hormone replacement therapy and oral contraceptives, both involving high-dose exogenous exposures, and not from "life-time" cumulative endogenous production. To the extent, therefore, that there is scientific evidence of a background or baseline risk, it exists only in circumstances involving sustained high-dose exogenous exposure.

32. Second, flowing from its erroneous conclusion that there is always a "background risk", the EC simply assumes that any additional exposure "may increase the risk of cancer". This claim suffers from at least two flaws: not all exogenous exposure alters endogenous levels (also referred to as background or circulating levels), which would at a minimum be required for risk to be altered; and even if background levels are altered, it is not automatic that "background risk" (were any to exist) would also be altered. With respect to the first point, Dr. Boobis explained how the body's system of homeostatic control compensates for variability in endogenous production and exogenous exposure. This system operates to ensure that endogenous hormone levels remain at the optimal level for a given physiological state. Additional exogenous exposure may result in compensation in the endogenous production such that the level remains unchanged. With respect to the second point, in light of natural variability in background levels, even if a given exogenous exposure leads to levels that are higher than would be present without that specific exposure, this will not necessarily be outside the range of normal variation, such that there will be any increase in any risk that may be present.

33. Third, the EC claims that these risks are "additive" regardless of the mode of action (*i.e.*, genotoxic or receptor-mediated). This is incorrect. Understanding the mode of action determines whether there is a threshold for adverse effects. In the case of these hormones, the mode of action of

[18] See Panel Questions to the Experts, Dr. Boisseau's reponse to Question 62, and Dr. Boobis' response to Question 62, at p. 58.

[19] EC's Responses after the Second Meeting, at para. 48 (emphasis added).

carcinogenicity (*i.e.*, receptor-mediated) is well established to have a threshold. And since there is a threshold, there is also an exposure below which there is no risk, and no amount of additional exposure changes that risk as long as that exposure remains below the threshold. To conclude, as does the EC, that all exogenous exposure alters background levels and that all changes in background levels alter background risks is simply a fundamental misrepresentation of the scientific evidence.

34. In fact, the EC appears to conflate the evaluation of risk with the evaluation of mere exposure. In paragraph 49, it reiterates that exposure to hormones from natural sources "cannot be avoided", then cites the Appellate Body finding in *EC – Hormones* that it is not arbitrary for governments to regulate natural sources differently from non-natural sources. However, the EC misinterprets the meaning of these findings by failing to acknowledge the difference between "exposure" and "risk". The Appellate Body findings only mean that once a substance has been identified as creating a risk, governments may be justified in reacting to that risk differently from natural sources than from non-natural sources. In this case, however, the EC has not demonstrated that there are risks from any source, natural or non-natural (other than sources that come in very high doses, *e.g.*, hormone replacement therapy), so it makes no sense to talk about avoiding one source and not the other. In other words, the EC is using the Appellate Body findings in an unjustified attempt to exempt itself from establishing the threshold question of whether there are risks from any source of these hormones. It attempts to reduce this question to whether the exposure is unavoidable (natural) or avoidable (non-natural), rather than whether there are risks from the substance from any source. Ultimately, the EC's whole argument about the "additive" nature of the risks is a secondary question to whether there are risks at all from normal exposures. On this point, the Experts have indicated that there are not.

35. A final point to be made about the EC's response is that the EC's references do not support its simplistic assertions. In paragraph 49, the EC cites Exhibit EC-35 to support the conclusion that the estrogenic activity of residues of phytoestrogens is seriously disputed. That may be the case. However, the article does not provide "indisputable" evidence that exposure to phytoestrogens "adds some more burden to background levels", nor does it support the conclusion that this addition "may increase the risk of cancer". For instance, the authors point out that the circulation concentration of isoflavones, a class of phytoestrogens, in infants fed soy-based formula are "13000-22000 times higher than plasma estradiol concentrations [in the same infants]".[20] The authors conclude:

> However, despite the concern derived from cell studies on endocrine effects of soy-based infant formulas, the clinicians continue to consider them a safe and nutritionally complete feeding option for most infants. There is no reported evidence of endocrine effects in humans from consumption of these soy-based formulas. Although these is indeed no indication of adverse effects of soy infant formulas to the newborn, the tremendous plasma concentrations of isoflavones after consumption have not yet been thoroughly evaluated with respect to biological relevance and should not be overlooked. [21]

36. The authors suspect that the high levels of isoflavones resulting from the consumption of soy-based infant formula should have a biologic effect, but cannot explain the absence of reported adverse affects. However, the absence of reported adverse effects contradicts the EC's speculative conclusion that "this addition may increase the risk of cancer." Indeed, to the contrary, there is no evidence that this particular addition has any impact whatsoever on the risk of cancer.

[20] Dolores Ibarreta, Andreas Daxenberger & Heinrich H.D. Meyer, "Possible health impact of phytoestrogens and xenoestrogens in food", at p. S409 (Exhibit EC-35).

[21] *Ibid.*, at p. S410.

37. Finally, in footnote 13, the EC criticizes the defending parties and JECFA for not being "aware [of Exhibit EC-35] when they evaluated these hormones", even though the study was published only in 2001, a full two years after JECFA considered the three natural hormones. This is all the more surprising given the fact that SCVPH itself practically ignores the article in its 2002 Opinion, thereby suggesting that the SCVPH did not consider the article to be sufficiently pertinent to the issues at hand.

Q12. A 1999 Report of the Committee for Veterinary Medicinal Products of the European Communities refers to the low bioavailability of oestradiol 17β. How is this finding reconciled with references to bioavailability in the SCVPH Opinion? (please refer to comments by the parties on the Panel's Question 43 to experts)

38. In response to this question, the EC attempts to undermine the scientific credibility of one of its own scientific bodies. One wonders how the CVMP would respond to this attack, particularly to the assertion that "the CVMP opinion must be simply reproducing on this point the JECFA evaluations of 1988 and 1999 for oestradiol-17β",[22] which suggests that the CVMP failed to exercise independent scientific judgment in assessing the bioavailability of oestradiol 17β.

39. In any event, the EC confuses the question of bioavailability with the question of whether all relevant residues of oestradiol 17β, in free and conjugated forms, including lipoidal (fatty acid) esters, and its metabolites have been adequately taken into account in determining residue levels. These are two separate questions. The low bioavailability of oestradiol 17β is not influenced by the fact that some saturated fatty acid forms of oestradiol 17β may not have been taken into account. Increasing the level of exposure to a substance does not increase its bioavailability. The EC is simply conceptually confused.

40. That being said, the question of whether all pertinent residues of oestradiol 17β, including lipoidal esters, have been taken into account was addressed in Exhibit EC-47, a study by D. Maume referenced in the 2002 SCVPH Opinion.[23] In characteristic fashion, the SCVPH fails to note that even if oestradiol 17β residues in the form of lipoidal esters are taken into consideration, the total oestradiol 17β exposure in meat from untreated and appropriately treated cattle meat is, respectively, 0.2% and 1.3% of the ADI! This is in the same range as JECFA's estimate of additional oestradiol 17β exposure from meat from treated animals (2% of ADI).[24] Thus, the calculations presented in the study relied upon by the SCVPH simply do not support its conclusion that "these data indicate that lipoidal esters … may contribute considerably to an additional oestrogen exposure via meats".[25]

41. In paragraph 56, the EC fails to understand the explanation provided by Dr. Boobis that the ADI is "bioavailability adjusted".[26] As the ADI is based on a No-observed-effect-level (NOEL) derived from a human study with an oral route of exposure, a change in our understanding of the bioavailability of a substance does not alter the ADI. The risk to prepubertal boys from eating eggs and drinking milk does not change because our calculations of the bioavailability of oestradiol 17β have changed from 5% to, for the sake of argument, 10% or 20%. It is unfortunate that at this late stage of the process the EC has not appeared to grasp this basic point.

[22] EC's Responses after the Second Meeting, at para. 53 (emphasis added).
[23] 2002 SCVPH Opinion, at p. 10 (Exhibit CDA-7).
[24] JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12, at p. 83 (Exhibit CDA-17).
[25] 2002 SCVPH Opinion, at p. 10 (Exhibit CDA-7).
[26] See Panel Questions to the Experts, Dr. Boobis' response to Question 43, at p. 40.

Q13. In its comments on replies of experts to Panel Question 19 (para.75) Canada asserts that a recent Opinion of the European Food Safety Agency (EFSA) recognizes thresholds for genotoxic substances. Please elaborate.

42. The EC in its response to this question attempts to explain away the very clear fact that even the EC's own regulatory agency accepts that there are genotoxic substances for which thresholds exist. The EC claims that the "other relevant parts" of EFSA's opinion somehow justify keeping the six hormones at issue here out of the food chain. The implications of the EFSA opinion on the EC's claims are not that even if oestradiol 17β is proven to be genotoxic *in vivo* it should still be added to the food chain, which seems to be how the EC has interpreted Canada's reference to the EFSA opinion. Oestradiol 17β has not been demonstrated to be genotoxic *in vivo*, so that is not the issue. Rather, EFSA's conclusion that genotoxic substances can exhibit a threshold contradicts the SCVPH's decision not to complete a dose-response assessment because of its conclusion that oestradiol 17β is genotoxic and hence does not exhibit a threshold. Therefore, even though it concluded (incorrectly, as Canada has explained elsewhere) that oestradiol 17β was genotoxic, its conclusion that there is no threshold, such that it need not conduct a dose-response assessment, was not justified.

Q14. Has the draft assessment of the UK Group (referred to in para.187 of the European Communities' rebuttal submission) already been assessed by EFSA or other relevant institutions? If so, what are the conclusions?

43. In response to this question, the EC again raises the issue of incomplete data and scientific uncertainty, this time in the context of selectively excerpted portions of the Final Report of the UK Veterinary Products Committee (June 2006) (VPC Report).[27] The EC fails, however, to quote the relevant conclusions of that report. For example, the report concludes that,

> Following a critical evaluation of the scientific reasoning and methods of argument adopted in the key papers and studies cited in the SCVPH 2002 Report, the Working Group were unable to support the conclusion reached by the SCVPH that risks associated with the consumption of meat from hormone-treated cattle may be greater than previously thought.[28]

44. The VPC Report further confirmed the non-controversial scientific finding that exposure to these hormones could have biological effects "if exposure is at a sufficiently high level"[29] and therefore concluded that "key issues" were the conduct of a dose-response assessment and an evaluation of the additional exposure from meat from treated animals. Therefore, contrary to the EC's claim that this report validates its ban, the report does the exact opposite. That is, it confirms that the EC's ban is not based on a risk assessment appropriate to the circumstances because the purported risk assessment on which the ban is based (*i.e.*, the SCVPH opinions) does not include a dose-response assessment.

45. Nowhere does the VPC Report corroborate the SCVPH's claim that any of the six hormones is mutagenic, which would be the minimum required for a risk assessor to decline to conduct a dose-response assessment. In fact, commenting on the SCVPH's own conclusions related to genotoxicity, the VPC Report concluded that "the studies on which the SCVPH based their Opinion were all non-standard studies …, or were unconvincing due to the absence of a dose-response".[30] Further on, the report indicated that most of these studies produced "information of questionable relevance to effects

[27] The Draft Report, which Canada understands is materially identical to the Final report released this summer, is Exhibit CDA-26.
[28] *Ibid.*, at p. 3.
[29] *Ibid.*, at p. 4 (emphasis added).
[30] *Ibid.*, at p. 24.

that may occur in the intact animal" and were of "poor quality".[31] The key study was found to suffer "methodological and interpretation flaws".[32] Echoing the advice of Dr. Boobis, the VPC Report finds that,

> Although there is evidence that oestrogen metabolites may be directly genotoxic *in vitro*, *in vivo* their formation is affected by opposing activation and inactivation metabolic pathways, the presence of anti-oxidants and DNA repair capacity and thus it is likely this genotoxicity will have a threshold response. … To date, there are no standard tests conducted *in vivo*, even on 17β-oestradiol metabolites, which indicate a mutagenic potential for 17β-oestradiol *in vivo*.[33]

46. While the EC selectively reproduces from the VPC Report quotations that identify other areas of research that could be pursued, or that indicate that the "definitive" risk assessment has not yet been completed, none of these "qualifications and reservations" justifies the conclusions drawn by the SCVPH. The VPC Report explicitly concluded this. In fact, the findings of the VPC Report are that a dose-response assessment is a required component of a risk assessment of these six hormones, something the SCVPH failed to do.

47. More evidence and information can be generated, of course, and the "definitive" risk assessment has not yet been completed. But as Dr. Boobis advised during the meeting with the Experts, it will always be possible to generate more evidence and information. However, risk assessors cannot let uncertainty about information they do not think they have keep them from making decisions based on the information they do have. And with respect to these six hormones, anyone who has evaluated the available information, and who is not associated in some fashion with the EC's hormones ban, has concluded that there are no risks from exposure to these hormones from meat from treated animals.

48. With respect to the EC's claim that the VPC Report further demonstrates the existence of scientific uncertainty, as Canada explained in its answer to Question 4 to the United States and Canada from the EC, there is no uncertainty about any issue that is relevant to the issue of whether or not the SCVPH's conclusions regarding these hormones are justified. While the VPC Report points to several issues about which more information would be useful, none of those issues justifies the SCVPH's failure to conduct a dose-response assessment with respect to oestradiol 17β, and certainly none of them justifies its failure to conduct a risk assessment at all with respect to the other five hormones.

Q15. What steps has the European Communities taken to request re-evaluation of the existing international standards for the five hormones, <u>according to the procedures of JECFA or Codex</u>? Please provide documentation.

49. In short, the EC's answer to this question confirms that it has not taken any steps to request the re-evaluation of the existing international standards for the five hormones, according to the procedures of JECFA or Codex. The EC's response is a creative attempt to recast in as favourable light as possible its failure to take these basic and straightforward steps.

50. Furthermore, the EC's criticism of JECFA's decision to re-evaluate the natural hormones in February 1999 is without merit. The EC faults JECFA for its "refusal to postpone for a period of 2-3 years" its February 1999 re-evaluation in order to await the outcome of the EC's 17 new studies.[34]

[31] *Ibid.*, at p. 27.
[32] *Ibid.*
[33] *Ibid.*
[34] EC's Responses after the Second Meeting, at para. 80.

This criticism is ill-founded for several reasons. First, given the position of the EC before the first panel and the Appellate Body in *EC – Hormones* that "new" evidence demonstrated that oestradiol 17β is a direct-acting genotoxic carcinogen, it is hardly surprising that JECFA would act immediately to review this "new" evidence.[35] Second, the EC is being hypocritical: after criticizing JECFA for "waiting" 10 years to re-evaluate carbadox, the EC now criticizes JECFA for not "waiting" to re-evaluate other substances, despite the alarmist position it adopted in the previous panel and appellate proceedings concerning "new" evidence. Lastly, recall that the SCVPH issued its first Opinion in April 1999, less than three months after JECFA's February 1999 re-evaluation, indicating that JECFA was not alone in its "refusal" to wait the two to three years for this "newer" evidence. We can only speculate as to the importance the SCVPH attached to the 17 studies, given its refusal to wait for their results.

51. One final point in relation to MGA. The EC, in objecting to the adoption of MRLs for MGA at the recent 66th JECFA meeting, reiterates the same old, tired objections concerning old data and the putative need for additional research.[36] In addition, the EC reiterates its mantra concerning the potential misuse of oestradiol implants, implying that misuse of MGA may pose safety risks. However, the EC's own evidence shows that (a) consumption of 10 times the maximum approved dose only slightly exceeds JECFA's ADI[37] and (b) a 3-fold and 10-fold increase in the approved dose of MGA reduces the levels of oestradiol 17β and estrone to below the levels found in control animals.[38] This is not compelling evidence of human health risks in the unlikely event that producers overdose their animals.

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[35] See Panel Questions to JECFA/Codex/IARC, JECFA's response to Question 20, at p. 2.

[36] EC's Responses after the Second Meeting, at paras. 82-83.

[37] See Panel Questions to the Experts, Dr. Boobis' response to Question 62, at p. 51, reviewing an article by Andreas Daxenberger concerning the misuse of MGA.

[38] M. Hageleit, *et al.*, "Dose-dependent effects of melengestrol acetate (MGA) on plasma levels of estradiol, progesterone and luteinizing hormone in cycling heifers and influences on oestrogen residues in edible tissues", at p. 852 (Exhibit EC-16) ("after three-fold treatment E_2-17β concentrations in plasma are reduced when compared with a normal cycle, but not completely decreased as apparent after 10-fold dose").

WORLD TRADE ORGANIZATION

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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex D to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex B: Add.2
- Annex C: Add.3
- Annex E: Add.5
- Annex F: Add.6
- Annex G: Add.7

ANNEX D

REPLIES OF THE SCIENTIFIC EXPERTS TO QUESTIONS POSED BY THE PANEL

A. GENERAL DEFINITIONS

1. Please provide brief and basic definitions for the six hormones at issue (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate), indicating the source of the definition where applicable.

Dr. Boisseau

1. Oestradiol-17β is the most active of the oestrogens hormone produced mainly by the developing follicle of the ovary in adult mammalian females but also by the adrenals and the testis. This 18-carbon steroid hormone is mainly administered as such or as benzoate ester alone (24 or 45 mg for cattle) or in combination (20 mg) with testosterone propionate (200 mg for heifers), progesterone (200 mg for heifers and steers) and trenbolone (200 mg and 40 mg oestradiol-17β for steers) by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter.

2. Progesterone is a hormone produced primarily by the corpus luteum in the ovary of adult mammalian females. It is administered to cattle, steers, usually at 200 mg in combination with oestradiol-17β or oestradiol benzoate (usually 20 mg) by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter.

3. Testosterone is a hormone produced primarily in the testes of adult mammalian males. This 19-carbon steroid has potent androgenic properties. It is administered as testosterone propionate (200 mg) in combination with oestradiol-17β or oestradiol benzoate (20mg) by a subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle. The ear is discarded at slaughter.

4. Melengestrol acetate is an orally active synthetic progestogen about 30 times as active as progesterone. It is used to improve body weight and feed conversion in female beef cattle. It is fed at daily doses of 0.25-0.50 mg per heifer usually 90-150 days prior to slaughter.

5. Trenbolone acetate is a synthetic steroid with anabolic properties several fold above that of testosterone. It is administered alone (300 mg for heifers) or in combination with oestradiol-17β (20 mg for calves and 40 mg for steers), by a subcutaneous implant to the base of the ear to improve body weight, feed conversion and nitrogen retention in cattle. It is administered to cattle 60-90 days or more before the intended date of slaughter. The ear is discarded at slaughter.

6. Zeranol, is a natural mycooestrogen derived from zearalenone produced by different species of fusarium molds. This non-steroidal anabolic agent is administered to cattle either alone (36 mg) or in combination with trenbolone acetate (140 mg) by subcutaneous implant to the base of the ear to improve body weight and feed conversion in cattle.

Dr. Boobis[1]

7. Oestradiol-17β is the most potent mammalian oestrogenic hormone. It is produced in the ovary, placenta, testis, and possibly the adrenal cortex *(ChemIDPlus Advanced, National Library of Medicine (http://chem.sis.nlm.nih.gov/chemidplus))*

8. Oestradiol-17β is the most potent form of mammalian oestrogenic steroids. In humans, it is produced primarily by the cyclic ovaries and the placenta. It is also produced by the adipose tissue of men and postmenopausal women (*PubChem, National Library of Medicine (http://pubchem.ncbi.nlm.nih.gov/)*

9. Progesterone is the principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle *(ChemIDPlus Advanced).*

10. Progesterone is the major progestational steroid that is secreted primarily by the corpus luteum and the placenta. Progesterone acts on the uterus, the mammary glands and the brain. It is required in embryo implantation, pregnancy maintenance, and the development of mammary tissue for milk production. Progesterone, converted from pregnenolone, also serves as an intermediate in the biosynthesis of gonadal steroid hormones and adrenal corticosteroids *(PubChem).*

11. Testosterone is a potent androgenic steroid and major product secreted by the Leydig cells of the testis. Its production is stimulated by luteinizing hormone from the pituitary. In turn, testosterone exerts feedback control of the pituitary LH and FSH secretion. Depending on the tissues, testosterone can be further converted to dihydrotestosterone or oestradiol *(PubChem).*

12. Trenbolone acetate is a synthetic steroid that has been used as an anabolic agent in veterinary practice. *(Martindale: The Complete Drug Reference (2006), Pharmaceutical Press, London).*

13. Zeranol is a naturally occurring metabolite of the mycotoxin zearlenone which is produced by a number of Fusarium fungal species. The commercial formulation contains specifically the α-isomer. Zeranol is a non-steroidal anabolic agent. (*JECFA (1988a). Toxicological Evaluation of Certain Veterinary Drug Residues in Food: WHO Food Additives Series 23, WHO, Geneva, Switzerland).*

14. Zeranol is a nonsteroidal oestrogen that has been used for the management of menopausal and menstrual disorders. It has also been used as a growth promoter in veterinary practice *(Martindale: The Complete Drug Reference).*

15. Melengestrol acetate (MGA) is an orally active 6-methyl progesterone acetate with reported glucocorticoid activity and effect on estrus *(PubChem).*

16. Melengestrol acetate is a progestogen that is used as an animal feed in beef heifers to improve feed efficiency, increase the rate of body-weight gain, and suppress oestrus (*Martindale: The Complete Drug Reference*).

Dr. Guttenplan

17. Oestradiol-17β: an estrogenic sex hormone, which in the female, functions in the ovarian cycle and maintains uterine health. In males it inhibits the synthesis of testosterone. A member of a

[1] A full list of references cited in responses from Dr. Boobis can be found in Attachment 1.

class of compounds called steroids (which, chemically, have three 6-membered rings and one 5-membered ring).

18. Progesterone: a steroidal anti-estrogen; used as a contraceptive and to correct abnormalities in the menstrual cycle.

19. Testosterone: a steroidal androgenic sex hormone, which in the male leads the production of sperm components. It is also important in promoting the development of secondary sex characteristics.

20. Trenbolone acetate: a synthetic anabolic (growth-stimulating) hormone, often used in cattle.

21. Zeranol: a synthetic nonsteroidal **growth promoter often used in cattle.**

22. Melengestrol acetate: a synthetic steroidal growth promoter often used in cattle. Also used for estrus synchronization in cattle.

(Opinion of SCVPH, 1999 (US Exhibit 4 part 1))

2. Please provide definitions for the following terms as they relate to the hormones at issue, indicating the source of the definition where applicable: anabolic agents, steroids, steroidal oestrogens, parent compounds/metabolites, catechol metabolites, mitogenicity, mutagenicity, androgenic/oestrogenic activity, genotoxicity, genotoxic potential, carcinogenicity, and tumorigenicity. In your replies, please be sure to identify and describe any relevant differences between the terms.

Dr. Boobis

Anabolic agent

23. The building up in the body of complex chemical compounds from smaller simpler compounds (e.g., proteins from amino acids), usually with the use of energy. Cf.: catabolism, metabolism. *Stedman's Medical Dictionary (2000), Lippincott Williams & Wilkins, Philadelphia, PA*

24. Testosterone, or a steroid hormone resembling testosterone, which stimulates the growth or manufacturing of body tissues. *Taber's Cyclopedic Medical Dictionary - 20th Ed (2005), F. A. Davis Company, Philadelphia, PA*

25. Anabolism: The processes of metabolism that result in the synthesis of cellular components from precursors of low molecular weight. *IUPAC(1997). Compendium of Chemical Terminology, 2nd Edition (http://www.iupac.org/publications/books/author/mcnaught.html)*

Steroids

26. A large family of chemical substances, comprising many hormones, body constituents, and drugs, each containing the tetracyclic cyclopenta[a]phenanthrene skeleton *Stedman's Medical Dictionary.*

Steroidal oestrogens

27. (Steroidal) compounds that produce the behaviour estrus ("the portion or phase of the sexual cycle of female animals characterized by willingness to accept the male"). *Hughes, C (1996). Are the*

differences between estradiol and other estrogens merely semantical? (Letter to the Editor). J Clin Endocrinol Metab 81:2405.

28. A more biochemical definition might be: compounds with a steroid structure that possess endocrine effects qualitatively similar to those of oestradiol-17β and that act through oestrogen receptors.

Parent compounds/metabolites

29. When related to exogenous compounds, the parent is the compound to which an individual is exposed. The relationship between parent compound and metabolite is that the parent serves as a substrate for biotransformation (enzymatic conversion) to yield a product that is chemically distinct from the parent, a metabolite *(A. Boobis).* With respect to metabolites of veterinary drugs, it is possible that the residue in meat comprises, at least in part, one or more metabolites of the drug used to treat the animals. Ingestion of such metabolites can lead to their metabolism in human subjects. Hence, there will be a parent/metabolite relationship even for such compounds.

30. Metabolite: Any intermediate or product resulting from metabolism. National Library of Medicine (1993). Glossary for Chemists of Terms Used in Toxicology (http://www.sis.nlm.nih.gov/enviro/glossarymain.html; Pure Appl Chem, 1993, 65, 2003-2122)

31. Metabolism: in a narrower sense, of drugs, one mechanism of clearance, is the irreversible biochemical transformation of a compound to another chemical (metabolite). The metabolite is usually more polar (water-soluble) and, therefore, more readily excreted, than the parent compound; thus, metabolism facilitates drug excretion. *Absorption Systems (2006). Glossary Terms (http://www.absorption.com/Site/Glossary/Default.aspx)*

Catechol metabolites

32. Any intermediate or product resulting from metabolism (enzymatic transformation) containing the core structure benzene-1,2-diol *IUPAC (1993). A Guide to IUPAC Nomenclature of Organic Compounds, Blackwell Science, Oxford, UK*

Mitogenicity

33. The property of an agent whereby it induces mitosis and cell proliferation. Mitosis is the process by which a cell nucleus divides into two daughter nuclei, each having the same genetic complement as the parent cell: nuclear division is usually followed by cell division *(NLM Glossary for Chemists of Terms Used in Toxicology).*

Mutagenicity

34. Ability of a physical, chemical, or biological agent to induce heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof).

35. Mutation: Any relatively stable heritable change in genetic material that may be a chemical transformation of an individual gene (gene or point mutation), altering its function, or a rearrangement, gain or loss of part of a chromosome, that may be microscopically visible (chromosomal mutation); mutation can be either germinal and inherited by subsequent generations, or somatic and passed through cell lineage by cell division. *NLM Glossary for Chemists of Terms Used in Toxicology*

Androgenic activity

36. Having the property to interact with androgen receptors in target tissues to bring about the effects similar to those of testosterone. Depending on the target tissues, androgenic effects can be on sexual differentiation; male reproductive organs, spermatogenesis; secondary male sex characteristics; libido; development of muscle mass, strength, and power.

37. Capacity to promote the development and maintenance of male sex characteristics. National Library of Medicine, Genetics Home Reference (http://ghr.nlm.nih.gov/ghr/glossary/Glossary)

Oestrogenic activity

38. Biological activity similar to that of an oestrogen.

39. Oestrogens cause the thickening of the lining of the uterus and vagina in the early phase of the ovulatory, or menstrual, cycle; in lower animals cyclical oestrogen secretion also induces oestrus, or "heat". The oestrogens are also responsible for female secondary sex characteristics such as, in humans, pubic hair and breasts, and they affect other tissues including the genital organs, skin, hair, blood vessels, bone, and pelvic muscles. *The Columbia Electronic Encyclopedia (2003), Sixth Edition, Columbia University Press, New York City, NY*

40. Oestrogenic activity can arise through several possible mechanisms, by mimicking natural oestrogens and interacting with oestrogen receptors, by affecting oestrogen-sensitive pathways by some other mechanism and by altering the levels of endogenous oestrogens, be changing the rate of synthesis or degradation. *Lintelmann J, Katayama A, Kurihara N, Shore L, and Wenzel A (2003). Endocrine disruptors in the environment (IUPAC Technical Report) Pure Appl Chem, 75, 631–681. Miyamoto J and Burger J (Editors) (2003). Special Topic Issue on the Implications of Endocrine Active Substances for Humans and Wildlife. Pure Appl Chem, 75: 1617-2615.*

Genotoxicity

41. Ability to cause damage to genetic material. Such damage may be mutagenic and/or carcinogenic. *NLM Glossary for Chemists of Terms Used in Toxicology*

42. Mutagenicity is a form of genotoxicity. However, not all genotoxicity is necessarily mutagenicity. Examples include adduction to DNA and damage to DNA that does not lead to heritable change. Whilst adduction can lead to mutation, the presence of adducts *per se* is a measure of genotoxicity and not of mutagenicity.

Genotoxic potential

43. Of a compound, it possesses characteristics such that it might be capable of causing genotoxicity (usually in vivo), based on considerations such as the results of tests in vitro. It remains to be determined whether genotoxicity is indeed expressed in vivo, i.e. that the potential is realized *(A. Boobis interpretation of usage by JECFA and elsewhere).*

Carcinogenicity

44. Process of induction of malignant neoplasms by chemical, physical or biological agents.

45. Malignant neoplasm: a population of cells showing both uncontrolled growth and a tendency to invade and destroy other tissues; a malignancy is life-threatening.

46. Neoplasm: new and abnormal formation of tissue as a tumour or growth by cell proliferation that is faster than normal and continues after the initial stimulus that initiated the proliferation has ceased. *NLM Glossary for Chemists of Terms Used in Toxicology*

Tumourigenicity

47. Process of inducing tumours, i.e. any abnormal swelling or growth of tissue, whether benign or malignant. *NLM Glossary for Chemists of Terms Used in Toxicology*

48. Hence, whilst a carcinogen produces tumours (which are malignant), tumourigenic agents do no necessarily produce malignant neoplasia.

Dr. Guttenplan

49. Anabolic agents: agents promoting build-up - in animals, usually muscle mass, in biochemicals, building larger molecules from smaller ones.

50. Steroids: Metabolites of cholesterol, containing three 6-membered rings and one 5-membered ring.

51. Steroidal oestrogens: Estrogens that contain the steroidal ring system.

52. Parent compounds/metabolites: in a chemical conversion, the initial chemical is called the parent compound and the product, the metabolite.

53. Catechol metabolites: Catechols are compounds containing a benzene ring with two hydroxyl groups on the benzene ring. When they are converted to a different compound, a catechol metabolite results.

54. Mitogenicity: Relating to or causing cell division.

55. Mutagenicity: Relating to or causing a change in DNA composition. May also relate to a change in protein structure

56. Androgenic activity: acting like a male sex hormone.

57. Oestrogenic: acting like a female sex hormone.

58. Genotoxicity: Relating to or causing damage to DNA.

59. Genotoxic potential: The possible ability of an agent to cause damage to DNA.

60. Carcinogenicity: Relating to or causing a process leading to cancer.

61. Tumorigenicity: Relating to or causing the formation of tumors. This term refers to tumor formation, whereas carcinogenicity may also refer to the process by which tumors are induced. (*Codex Microbiological RA*).

B. RISK ASSESSMENT TECHNIQUES

3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

Dr. Boisseau

62. To my knowledge, there is no international guidance document relevant to the conduct of a risk assessment with respect to veterinary drug residues. Currently, there is no Codex guidance document relevant to the conduct of a risk assessment with respect to veterinary drug residues. The situation is similar in the European Union. The CVMP has assessed all the pharmacologically active substances used in veterinary medecine without any written guideline about risk assessment.

63. I have proposed some 15 years ago to CCRVDF (Codex Committee on Residues of Veterinary Drugs in Food) to develop and adopt a guidance about risk management including a risk assessment policy. In its last session held in May 2006 in Cancun, Mexico, CCRVDF has decided to propose to the Codex Committee on General principles (CCGP) and to the Codex Commission a draft project concerning a rationale about the risk analysis to be implemented by CCRVDF. This draft project includes two parts: (1) a procedure with the interactions between CCRVDF, responsible for risk management, and JECFA (Joint Expert Committee on Food Additives) responsible for risk assessment, with, in annex, the format to be used by member states for establishing a risk profile; (2) the principles of a risk assessment policy.

Dr. Boobis

International guidance documents

64. The following guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues are available:

WHO (2001): Residues of veterinary drugs in food (current version Jan 2001).

WHO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives

WHO (1996): Residues of veterinary drugs in food (current version August 1996) Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives

Residues of veterinary drugs in food (Sept 2002)

FAO (2002a) procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives

Procedures for Recommending Maximum Residue Limits – Residues of Veterinary Drugs in Food (1987-1999) (FAO, 2000a)

Envionmental Health Criteria (EHC) 70: Principles For The Safety Assessment Of Food Additives And Contaminants In Food (IPCS, 1987)

Environmental Health Criteria (EHC) 104: Principles For The Toxicological Assessment of Pesticide Residues In Food (IPCS, 1990)

65. Also available are relevant sections from General Consideration Items in JECFA reports, which document guidance developed by JECFA over the years and are provided as an ongoing update to its risk assessment procedures (relevant volumes of WHO Technical Report Series).

66. Codex publishes a Procedural Manual that contains generic guidance on risk analysis and risk assessment policies. This is updated regularly, the latest version (15th) having been published in 2005: *Codex Alimentarius Commission (CAC) (2005). Procedural Manual, Fifteenth edition, WHO and FAO, Rome, Italy (ftp://ftp.fao.org/codex/Publications/ProcManuals/Manual_15e.pdf).*

67. Codex is currently developing a risk assessment policy for recommending maximum residue limits for veterinary drugs in food. To my knowledge this is still in the drafting stage (see JECFA, 2006a).

CCRVDF (2005). Risk Management Methodologies, Including Risk Assessment Policies in the Codex Committees on Residues Of Veterinary Drugs in Foods (ftp://ftp.fao.org/codex/Ccrvdf16/rv16_10e.pdf).

JECFA (2006a). Summary and Conclusions of Sixty-sixth meeting (Residues of veterinary drugs), Rome, 22-28 February 2006 (http://www.who.int/ipcs/food/jecfa/summaries/summary66.pdf)

4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)].

Dr. Boisseau

68. The European Communities is right when it says that "there is no Codex standard specifically on the risk assessment of effect of residues of veterinary drugs". In the conduct of its risk assessment with respect to the hormones at issue, as for all the other pharmacologically active substances used in veterinary medecine, JECFA has followed the general rationale used by all the countries which have assessed the safety of veterinary drug residues. This rationale has been internationally harmonised through scientific conferences and it is possible to say that there was an international non written agreement on this rationale. Nevertheless, the International Programme on Chemical Safety (IPCS) has sponsored in the 1980s the preparation and the publication of the Environmental Health Criteria (EHC) monograph No 70 entitled " Principles for the safety assessment of food additives and contaminants in foods". Then, JECFA has, in its meetings, regularly developped and consolidated the principles of this monograph EHC No 70 but it has never published the outcome of this work in any official document or monograph on risk assessment of veterinary drug residues, the only exception being for microbiologicals.

Dr. Boobis

Codex standards for risk assessment

69. It is not clear what is meant by the EC assertion that there is "no Codex standard specifically on the effects of residues of veterinary drugs", but a general one on microbiological assessment. It is certainly true that there is no detailed guidance manual from Codex on the assessment of the effects of residues of veterinary drugs. However, there are guiding principles in place, that have been in existence since before 1999. These relate to the procedures for risk assessment, the implications and meaning of an ADI (Acceptable Daily Intake) and procedures for setting MRLs. As indicated above, JECFA was guided by a number of relevant documents in its risk assessment procedures. JECFA developed an approach to the risk assessment of residues of antimicrobials, which was novel and not covered in detail in such guidance. Specific guidance was therefore developed by JECFA and adopted by Codex. In contrast, the approaches used in the assessment of the hormones followed

established risk assessment principles for toxicologically (as opposed to microbiologically) active compounds.

Dr. Guttenplan

70. It is correct that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs".

71. A monograph "TOXICOLOGICAL EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD" WHO Food Additives Series: 43, Prepared by the Fifty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) describes the data used to determine the ADI for estradiol, progesterone and testosterone. The principles of risk assessment (described below) were used in determining ADI's for estradiol, progesterone, and testosterone.

5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) and explain how they differ.

Dr. Boisseau

72. The following brief description of the three components of a risk assessment exercise is given with respect to veterinary drugs residues likely to be present in food of animal origin.

73. Risk assessment is a procedure run by persons having the relevant scientific and technical expertise. It is intended to determine the likelyhood and the gravity of any unexpected unwanted effect for the consumer which may result from the ingestion of veterinary drugs residues likely to be present in food of animal origin. Only scientific data, relevant with regard to assessing this risk, have to be taken into consideration in this procedure. In the Codex procedure, JECFA is responsible for conducting the risk assessment for veterinary drug residues.

74. Risk management is a procedure run by persons having political or administrative responsabilities. It is intended to protect consumers from any problem of public health associated with veterinary drugs residues likely to be present in food of animal origin. Other criteria than scientific ones, such as economical, sociological, cultural etc., can be taken into consideration in this procedure. Usually, this procedure leads to regulatory and/or administrative decisions.

The risk management procedure usually implies four steps:

(1) Risk evaluation

- identification of a food safety problem
- establishment of a risk profile
- ranking of the hazard for risk assessment and risk management priorities
- establishment of a risk assessment policy
- commissioning of risk assessment
- consideration of the results of the risk assessment

(2) Assessment of the different possible risk management options

- identification of the different possible risk management options
- selection of the preferred risk management option
- final risk management decision

(3) Implementation of the risk management decision

(4) Monitoring and review

- assessment of the effectiveness of the measures taken
- review of risk management and /or risk assessment as necessary

75. The risk management procedure has been considered by a joint FAO/WHO expert consultation in 1997.

76. In the Codex procedure, Codex is responsible for conducting the risk management for veterinary drug residues.

77. Even if communication between persons responsible for the risk assessment and the risk management is desirable and useful, scientific persons running the risk assessment procedure must be in the position to perform their work without any influence from the persons having political or administrative responsabilities. In order to guarantee their independence, these scientific persons, very often, carry out their work within independent agencies, at national or regional level. JECFA is an expert committee independent from the Codex. It carries out, among others, the risk assessment for veterinary drug residues on the request of Codex. Codex, including the CCRVDF and the Codex Commission, is, together with the member states, involved in the risk management. Risk assessors have to publish the conclusions of the risk assessment they have performed. JECFA does through monographs on toxicology and residues published respectively by WHO and FAO. Risk assessors may, in their conclusions, address some recommandations to the persons/bodies responsible for the risk management but they have not the power to take any regulatory or administrative decision.

78. Risk communication is an interactive process of exchange of informations and opinions on the potential risks associated with veterinary drug residues likely to be present in food of animal origin, among

(1) Risk assessors

(2) Risk managers

(3) Other interested parties such as

- consumers
- veterinarians
- technicians in animal husbandry
- animal owners
- animal health industry
- food processing industry

Risk communication should, among others,

- promote awareness and understanding of the specific issues under consideration during the risk analysis

- promote consistency and transparency in formulating risk management options/recommendations

- provide a sound basis for understanding the risk management decisions proposed

– improve the overall effectiveness and efficiency of the risk analysis

79. Scientific persons in charge of the risk assessment procedure are responsible of the communication on the issues associated with the risk assessment and the persons having political or administrative responsabilities are responsible of the communication on the issues associated with the risk management.

80. The risk communication has been considered by a joint FAO/WHO expert consultation.

Dr. Boobis

Components of risk analysis

81. The three components of a risk analysis exercise can be described as follows:

Risk Assessment

82. A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.

From IPCS (2004). Risk Assessment Terminology, WHO, Geneva (http://www.iseaweb.org/ipcsterminologyparts1and2.pdf)

Risk Management

83. The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

84. Risk management comprises three elements: risk evaluation; emission and exposure control; and risk monitoring.

From *Codex Alimentarius Commission(2005). 15th Procedural Manual*

Risk Communication

85. The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

From *Codex Alimentarius Commission (2005). 15th Procedural Manual*

86. Risk assessment is a scientific process in which the data are evaluated and on this basis, together with weight of evidence and expert judgment a conclusion is reached as to the nature of the hazards, the potential risk to exposed individuals and the extent to which exposure (measured or estimated) approaches those levels considered to be without appreciable risk. The output of the risk assessment is a health based guidance value, the allowable daily intake (ADI), in the case of a veterinary drug residue in food. An important aspect of risk assessment is to identify and describe the uncertainties associated with the evaluation. The MRL is an exposure level that it compatible with

both health protection and good veterinary practice. The ADI does not determine the MRL recommended by JECFA for consideration by Codex. However, in the risk characterization stage of risk assessment, comparison of exposure based on GVP (good veterinary practice) resulting in levels at the MRL, with the ADI establishes whether the exposure is adequately protective. If not, the risk assessment may be refined, or the conclusion may be that it is not possible to establish an MRL such that exposure would be consistent with public health protection.

87. Risk management is not a scientific process but a procedure whereby policies are established with respect to the use and acceptability of, in this case, a veterinary drug, compatible with protection of the public, good veterinary practice and efficacy and ensuring fair trade. Hence, the output of a risk assessment is one input to risk management decision-making. However, it is not the only one, as indicated above. Issues such as the veterinary need for the product and the security of the food supply may also be considerations. Normally, the risk manager accepts the output of the risk assessor, as this is the conclusion of the scientific experts in the field. There should be a clear separation between risk assessment and risk management. That is not to say that there should be no communication, but that the conclusions of the risk assessors should be their own, uninfluenced by any policy needs of the risk manager. Similarly, the risk manager should accept the conclusions of the risk assessor, unless there is a transparent reason to challenge them. If the risk manager chooses a course of action that is more, or less, precautionary than that justified on the basis of the risk assessment, the reasons for this should be clear and distinct from the risk assessment.

Dr. Cogliano

88. Risk assessment is the use of scientific data to describe the adverse effects of exposure to hazardous agents. Risk communication is the art of explaining these risks to different audiences. Risk management is the process of considering a risk along with other factors (for example, legal mandates, technical feasibility, cost, equity, and social norms) and making a decision about whether and how to mitigate the risk. The three are separate activities carried out for separate purposes.

Dr. Guttenplan

89. Risk Assessment is defined as the scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization. It basically attempts to evaluate risk.

90. Risk Management is defined as the process of weighing policy alternatives in the light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures. It basically refers to dealing with the hazard, generally to reduce risk.

91. Risk Communication is defined as the interactive exchange of information and opinions concerning risk and risk management among risk assessors, risk managers, consumers and other interested parties. It is basically concerned with making known the risks to interested and/or affected parties. (Codex Microbiological RA).

6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

Dr. Boisseau

92. The brief description of the four steps of a risk assessment procedure is given with respect to veterinary drugs residues likely to be present in food of animal origin. These four steps are:

(1) hazard identification, (2) hazard characterization, (3) exposure assessment, (4) risk characterization

93. The goal of the hazard identification is (1) to identify all the residues of the veterinary drugs under review likely to pose problems of health to consumers. The residues of concern for this substance imply both the parent compound and all the pharmacologically active metabolites derived from this parent compound; (2) to determine the concentrations of all these residues in the different edible tissues and products derived from animals treated by this veterinary drug; (3) to determine the evolution over the time of the concentrations of all these residues in the different edible tissues and products after animals have been treated by this veterinary drug; (4) to identify the marker residue to be used for the monitoring of residues in order to be sure that the animal derived food intended to the human consumption does not contain concentrations of residues exceeding the MRLs established for this veterinary drug.

94. The goal of the hazard characterization is to assess qualitatively and quantitatively all the adverse effects associated with the residues of veterinary drugs which may negatively impact the health of consumers or the environment. An important component of this step is to ascertain wether or not it is possible to establish a dose-effect relationship and a threshold which is the quantity of residues under which no adverse effect towards the health of consumers can be expected. The outcome of this step is, when possible, to establish a NOAEL (No Observed Adverse Effect Level) from the scientific data base available and to derive an ADI (Acceptable Daily Intake) from this NOAEL using an appropriate safety factor, the value of which depends on the toxicological profile of the residues. The NOAEL is the highest quantity of the veterinary drug at issue which is not associated with any adverse effect in toxicity tests carried out in animals or in studies carried out in humans.The ADI represents the maximum amount of residues of concern for the veterinary drug under review which can be daily ingested by consumers over a life time without any risk for their health. NOAELs and ADIs are expressed in mg or μg/kg/day.

95. The goal of the exposure assessment is to assess quantitatively the exposure of consumers to the residues of the veterinary drugs under review through the consumption of food of animal origin. This exposure os determine through a standard food basket determined by JECFA which encompasses mainly 500g musle, 100g liver, 50g kidney, 50g fat, 1,5l milk and 100g eggs.

96. In general terms, the goal of the risk characterization is to assess qualitatively and quantitatively the likelihood and the gravity of a given hazard for a human population exposed to this hazard. This assessment is based on the conclusions of the three former steps of hazard identification, hazard characterisation and exposure assessment. In the specific case of veterinary drug residues, this step does not exist as the goal of the risk analysis for these compounds is not to assess qualitatively and quantitatively the likelihood and the gravity of the adverse effects for the health of consumers associated with the veterinary drug residues they are exposed to through the animal derived food but to protect consumers' health from any adverse effect associated with these residues. In order to do so, MRLs are established , when possible. MRLs represent the highest concentrations of the residues of concern which can be accepted for the different edible tissues and products derived from the animals treated by the veterinary drug under review so that the quantity of residues daily ingested by consumers does not exceed the established ADI. This establishment of MRLs, aimed at providing an efficient protection of consumer health, is, therefore, a component of the risk management. Thus, when JECFA proposes MRLs to CCRVDF, it is also involved in a risk management component of the risk analysis procedure but, as these MRLs have to be adopted by Codex (CCRVDF and Commission), Codex is really, together with the member states, the body responsible for the risk management.

Dr. Boobis

Four steps of risk assessment

97. The four stages of risk assessment are as follows *(IPCS (2004). Risk Assessment Terminology):*

Hazard Identification

98. The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. This has been described as the intrinsic toxicological properties of the compound.

Hazard Characterisation

99. The qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. It also entails determining whether or not there is a threshold for the toxicological effect, i.e. a dose below which no effect occurs.

Exposure Assessment

100. The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant (*Codex Alimentarius Commission (2005).*

Risk Characterisation

101. The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions.

Dr. Guttenplan

102. Hazard identification is defined as the identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods. It is concerned with recognizing potential harmful agents. Hazard characterization is defined as the qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with the hazard. Exposure assessment is defined as the qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant. It basically attempts to estimate the quantity of the agent to which individuals or populations are exposed. Risk characterization is defined as the process of determining the qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment. For instance the risk of lung cancer in smokers is 1 in 10. (Codex Microbiological RA).

7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations, in your view, addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? Have they been addressed in the

1988 and 1999 JECFA risk assessments of these hormones? [see Canada's comments in para. 72 of its Rebuttal Submission]

Dr. Boisseau

103. The EC statement in para. 140 of the EC Replies to Panel questions indicating that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization (the level of exposure amounts proportionally to the level of risk for a given hazard) (and therefore they) have serious limitations in non linear situations, such as in the current case regarding hormones" refers to the genotoxic effect of oestradiol-17β and expresses the view that, for this hormone, a threshold should not be set. This situation is addressed by the risk assessment guidance currently under discussion within the CCRVDF. In 1987 and 1999, at the time of the assessment of oestradiol-17β, there was no risk assessment guidance available on this issue. Nevertheless, JECFA was perfectly aware about this kind of non linear situations. Thus, in 1987 and 1989, although the relevant data bases were not complete, JECFA considered that, for compounds such as Chloramphenicol, associated with aplasic anemia, and genotoxic nitroimidazole compounds such as Dimetridazole and Ronidazole, it was not possible to establish an effect/dose relation, and decided to base its conclusions on a qualitative risk assessment and did not recommend any ADI for these compounds.

104. In its 32nd session held in 1987, JECFA did not address this kind of non linear situation for oestradiol-17β because it concluded that the tumorigenic effect associated with this compound was related to its hormonal activity and that it was therefore possible to consider a threshold in this case.

105. If, in 1999, the 52nd JECFA recognized that oestradiol-17β "has a genotoxic potential", it concluded nevertheless that "the carcinogenicity of oestradiol-17β was probably a result of its interaction with hormonal receptors". Therefore, it did not take into consideration a non linear situation in its risk assessment and decided to confirm its conclusions made in 1987 and to establish an ADI of 0-0.05 μg/kg of body weight.

Dr. Boobis

Deterministic risk assessment

106. This question presupposes a specific outcome of the risk assessment, that there is no threshold for the toxicological effects of the hormones. The JECFA risk assessment concluded that the dose-response relationship for all of the endpoints was non-linear and that there was a threshold dose below which there was no appreciable risk over a lifetime of exposure. Hence, a deterministic approach, via the establishment of ADIs, was appropriate according to the procedures followed by the Committee. Should the Committee have concluded that the dose-response relationship was linear and that there was no dose below which there was no appreciable risk, there would have been two options. These would have been to have declined to establish an ADI on the basis that no exposure would be acceptable. The second would have been to establish a margin of exposure below which exposures would have been judged to pose a minimal (though non-zero) risk. Such an approach has recently been formalised *(IPCS (2005). Draft ECH, Principles for Modelling Dose-Response for the Risk Assessment of Chemicals, WHO, Geneva, Switzerland*) and was utilized by JECFA for its evaluation of certain contaminants in 2005 *(JECFA (2006b). Evaluation of Certain Food Contaminants, WHO Technical Report Series 930, WHO, Geneva).* In practice, it is likely that as veterinary drug residues in food are avoidable by not using the drug, the Committee would have declined to establish an ADI.

8. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please identify and describe any steps that

are taken in the risk assessment process to build a margin of safety into the final recommendation.

Dr. Boisseau

107. The procedure followed by JECFA for establishing ADIs and recommending MRLs includes three steps.

108. Establishment of a no observed adverse effect level (NOAEL) . This NOAEL is established after JECFA has considered the data obtained from all the available in vivo toxicity studies run in laboratory animals and from all the epidemiological studies and observations carried out in humans. JECFA considers also all the available in vitro tests, such as batteries of mutagenicity tests, which are likely to make easier the understanding of the mechanism of action of the toxicological effects of the veterinary drug under review. For each of these studies, except for in vitro tests, JECFA establishes a NOAEL which is the highest dose of the veterinary drug under review which is not associated with an observed adverse effect in humans or in animals. When the review of all these studies is completed, JECFA adopts, among the different NOAELs established for these studies, the final NOAEL which, once combined with an appropriate safety factor, will lead to the most conservative, the lowest, ADI.

109. Establishment of an ADI (Acceptable Daily Intake) in humans. ADI is the highest quantity of residues of the veterinary drug under review which can be daily ingested over a life time by consumers through animal derived food which will not pose a problem of health. JECFA derives such an ADI from the established NOAEL by using a safety factor. The value of this safety factor depends on the nature of the toxic effect associated with the NOAEL finally adopted by JECFA. If the NOAEL is derived from an in vivo toxicological study run in a laboratory animal, the value of such a safety factor is usually 100 as it associates two 10 safety factors. The first 10 safety factor is for the extrapolation from this laboratory animal to human as it is assumed, for caution reason, that humans may be 10 times more sensitive to this toxic effect than the laboratory animal involved in the study. The second 10 safety factor is for taking into consideration the diversity of humans, resulting from the sex, age, race, which can lead to a different sensitivity with regard to this toxic effect. If the toxic effect associated with the NOAEL finally adopted by JECFA is considered as being serious, as long as it is nevertheless still possible to consider that this toxic effect is compatible with a linear situation and the establishment of a threshold, the value allocated to the safety factor can be higher, up to 1000. On the contrary, if the adverse effect, associated with the NOAEL finally adopted by JECFA, is only derived from observations made in humans, the value of this safety factor, for exemple in the case of a reversible physiological effect, can be 10. In conclusion, the value of an ADI is usually 100 times less than the value of the corresponding NOAEL but may be also much lower.

110. Proposal of MRLs (Maximum Residue Limits). As an ADI is the final end point of the risk assessment procedure, there is a need for an operational tool which offers a practical way to be sure that this ADI will not be exceeded. That is the reason for which MRLs, already defined in my reply to the question No 6, are established so that it is possible for analytical laboratories to check that animal derived food do not contain residues of the veterinary drug under review in such amounts that the established ADI would be exceeded. In order to establish these MRLs for all the different edible tissues and products derived from the animals treated by the veterinary drug under review, JECFA uses a very conservative estimation of the human consumption of these tissues and products which represent an important additional safety factor. This food basket has been already described in my reply to the question No 6. Thus, MRLs are established in such a way that the quantities of residues potentially daily ingested resulting from this theoritical consumption of animal derived food do not exceed the value of the corresponding ADI. In addition, when it is not possible, for a veterinary drug under review, to identify and quantify all the residues associated with the toxic effect of concern, JECFA uses an additional safety factor in considering that all the residues derived from this veterinary drug have the same potential toxicity. On the other hand, all the residues which have not been proven

as being non bioavailable after oral ingestion are considered among the residues of concern. It is of special importance for the three natural hormones which are poorly bioavailable through oral route.

111. In conclusion, in order to build a margin of safety into the final recommendations, JECFA includes at different steps of its risk assessment the following different safety factors:

(1) establishment of ADI: humans are 10 times more sensitive than the animals involved in the most sensitive toxicity test; some humans may be 10 times more sensitive than others with regard to this toxic effect; the value of the safety factor can be increased in case of some serious adverse effects,

(2) exposure assessment: the human consumption of animal derived food is definitively overestimated,

(3) MRLs establishment: all residues, which are not clearly demonstrated that they are not associated with the toxic effect on which the ADI is based, are considered as being as toxic as the metabolite responsible for this toxic effect. All residues, which are not clearly demonstrated as being not bioavailable via oral route, are also included in the daily intake of residues of concern.

Dr. Boobis

JECFA procedure for establishing ADIs and MRLs

112. The procedure adopted by JECFA to establish ADIs is as outlined in the guidance on risk assessment principles (*Codex Alimentarius Commission (2005)*; see also my reply to question 3 above). Specifically, the hazard identification involved a systematic examination of the studies in experimental animals, together with studies in humans, where available and in vitro studies as appropriate. The extent of these varied with the hormone, being much greater with the natural hormones than with the synthetic ones. Human studies comprised epidemiological investigations, clinical trials and experimental studies. This evaluation enabled the range of effects of the compounds to be identified. In the hazard characterization stage, the mode of action and the dose-response curve for the toxicological endpoints were determined, to the extent possible. Understanding the mode of action helped inform the interpretation of the dose response relationship. Hence, once the Committee had concluded on the weight of evidence that the carcinogenic effects observed were most likely due to an endocrine mode of action, the identification of a threshold in the dose-response relationship was consistent with this. The dose at which no effect could be observed for each endpoint was determined (NOAEL) by inspection of the data, and failing that the dose producing the lowest observable adverse effect was identified (LOAEL). These data were used as the starting points (points of departure)for the derivation of the ADIs. To allow for human interindividual variability due either to differences in sensitivity (dynamics) or kinetics, a 10-fold factor was applied. When extrapolating from studies in experimental animals an additional 10-fold factor was applied to allow for possible inter-species differences in dynamics and kinetics. If a LOAEL was used an additional factor of up to 10 was used, depending on dose spacing, the shape of the dose-response curve above the LOAEL, and the magnitude of the response. Finally, where there was an identifiable sub-group who might reasonably be expected to be more sensitive than the group in whom data were obtained, for example children relative to adults, an extra factor was applied. Exposure assessment was based on determining residues in edible tissues after controlled trials in cattle. Using radiolabel, unless there was evidence to the contrary, all radioactive material was assumed to be parent and biologically active (e.g. for MGA *(*see *JECFA (2000a). Residues of Some Veterinary Drugs in Foods And Animals, FAO Food and Nutrition Paper 41/13, FAO, Rome)*. This is a cautious assumption, as often some or even most of the radiolabel is in the form of biologically less active or inactive metabolites *(*see *JECFA (2004). Residues of Some Veterinary Drugs in Foods And Animals, FAO Food and Nutrition*

Paper 41/16, FAO, Rome). Standard food consumption figures were used for different segments of the population, which again were relative conservative. Using these data the predicted exposure of high consumers was obtained, i.e. theoretical maximum daily intakes (TMDIs). In risk characterization, comparison of the estimated exposure (TMDI) with the ADI showed whether lifetime exposure at the levels predicted would be expected to be associated with any appreciable risk of adverse effects. This was undertaken for different age groups within the population. For all of the hormones under consideration, the estimated daily intake was well below the ADI, and hence use according to GVP would be without appreciable risk. Steps where a margin of safety is built in to the procedure are indicated above. However, to emphasize a few of these: risk assessment is based on the most sensitive endpoint, it assumes high level consumption over a lifetime, it often assumes that all of the residue is as active as the parent, default safety factors are used which are generally conservative.

9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

Dr. Boisseau

113. The Canadian statement stipulating that "it is recognized that JECFA only allocates an ADI for a food additive or a veterinary drug under review when JECFA considers that its scientific data base is complete and that there is no outstanding scientifific issue" is correct.

Dr. Boobis

Influence of completeness of scientific database on establishing an ADI

114. I would qualify the statement that "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues" as follows: This is certainly normally the case, but there are exceptions. The critical issue is whether a sufficiently cautious default can be adopted in the absence of certain information. For example, there may not be a NOAEL in a study, but it might be judged acceptable to use the LAOEL with an additional safety factor of up to 10. Similarly, the nature of the residue might not be fully defined in which case it would be assumed that it was all as active as the most active moiety, often the parent compound. As often some of the reside will be less active or inactive metabolites, this assumption is generally conservative. Hence, JECFA would require a complete data base unless it could adopt default assumptions that would if anything lead to a more conservative risk assessment than would be the case otherwise.

10. In paras. 129 and 168 of its Replies to the Panel Questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not". Does Codex have risk management options other than (1) the establishment of an MRL, (2) establishment that an MRL is not necessary or (3) no recommendation?

Dr. Boisseau

115. As already written in my replies to the questions No 5 and 6, JECFA is only responsible for conducting the risk assessment and Codex is responsible for conducting the risk management even if JECFA is also partly involved in the risk management in proposing MRLs to Codex. To my knowledge, Codex has no other risk management options concerning veterinary drug residues than (1) the establishment of a MRL, (2) establishing that a MRL is not necessary, (3) no recommandation.

116. Nevertheless, as already said in my reply to the question No 7, when JECFA decided that it was not possible to propose any ADI for Chloramphenicol and nitroimidazole compounds, it suggested to Codex that efforts should be made to replace or prohibit the use of these veterinary drugs.

11. What should, in your view, be the components of a qualitative risk assessment, compared with a quantitative risk assessment? [see para. 82 of Canada Rebuttal Submission]

Dr. Boisseau

117. A qualitative risk assessment should be based on the following components: (1) hazard identification, (2) hazard characterization and (3) qualitative exposure assessment. A qualitative risk assessment can be applied to a veterinary drug for which it has been demonstrated that (1) according to the hazard identification step, it leads to residues in animal derived food, (2) according to the hazard characterisation step, some of these residues are responsible of an adverse effect (a) which, such as genotoxicity, can not be associated with a relation effect/dose, (b) which can be expressed in humans, (c) for which it is not possible to establish a threshold under which an amount of residues, even very limited, cannot generate this adverse effect in humans, (3) according to the exposure assessment step, consumers are likely to ingest these residues through animal derived food.

118. As already said in my reply to the question No 7, JECFA based its conclusions on such a qualitative risk assessment for chloramphenicol, dimetridazole and ronidazole and did not recommend any ADI for these compounds.

Dr. Boobis

Qualitative versus quantitative risk assessment

119. The risk assessment paradigm is such that it is not appropriate to conduct a qualitative risk assessment *a priori*. This is because such an assessment requires knowledge of hazard and mode of action, either determined experimentally or assumed. Hence, a qualitative assessment might be undertaken after conducting at least part of a conventional risk assessment, when it was apparent, or assumed, that there was no exposure that did not pose some risk and thus establishing a safe dose (an ADI) would not be possible.

120. Hence, a qualitative risk assessment should comprise all four steps of the conventional risk assessment paradigm, but with certain differences. There would still be need of hazard identification and some form of hazard characterization. During hazard characterization, if possible, the mode of action should be determined through mechanistic considerations. The potential relevance of this to human risk should be considered. Where mode of action cannot be established, human relevance is assumed in the absence of evidence to the contrary. Certain modes of action are considered to possess no threshold based on the intrinsic hazard (most notably DNA-reactive genotoxicity). For compounds exhibiting such properties it is assumed that there is no threshold for the response. In such circumstances, current practice in many regions, including WHO and the EU, would be that it would be inappropriate to derive a health based guidance value (ADI), as any exposure would be considered to pose a risk. The need for detailed dose-response analysis would be questionable. However, in a risk assessment, as opposed to risk management, there is still need for scientific rigour. Hence, the conclusion that exposure is irrelevant because of the nature of the effect is a risk management decision. In risk assessment, even if establishment of an ADI is considered inappropriate, it would be of value to risk managers to provide a margin of exposure estimate, to determine how great the risk is likely to be. This would require exposure assessment. This would be of help in considering the relative risk compared with background exposure, particularly for compounds occurring

endogenously. Finally, risk characterization would be necessary to consider the relevance of experimental observations to humans. There may be kinetic or dynamic factors indicating that although theoretically there was no exposure with zero risk, in practice the risk would be minimal and therefore acceptable (e.g. PPR Opinion on daminozide, which contributed to EC decision to approve annex 1 listing of the compound .*(PPR (2004). Opinion of the PPR Panel related to the evaluation of daminozide in the context of Council Directive 91/414/EEC (May 2004) (http://www.efsa.eu.int/science/ppr/ppr_opinions/453_en.html; Official Journal L 241 , 17/09/2005 P. 0051 – 0056))*

Dr. Cogliano

121. The components of a qualitative risk assessment are (1) a critical review of the pertinent scientific information on an agent and (2) an evaluation of the weight of the evidence that the agent can alter the risk of one or more adverse effects.

122. Paragraph 82 of Canada's Rebuttal Submission seems confused about the role of dose-response analyses in a qualitative assessment. A qualitative risk assessment can consider the presence or absence of dose-response relationships in evaluating epidemiological and experimental information. For example, the *IARC Monographs* do this in their evaluations of whether an agent can alter the incidence of cancer in humans. This is a completely different matter from estimating the dose of an agent that may provoke a specific level of adverse effect. This latter activity is part of quantitative risk assessment and it can be delineated as a separate activity from the qualitative risk assessment.

12. How is scientific uncertainty addressed in risk assessments in general? With respect to the assessment of risks from the consumption of meat treated with the growth promotion hormones at issue, how has scientific uncertainty been considered by JECFA/Codex? How does it differ from the way it has been considered by the European Communities in its assessment of risks from the consumption of meat treated with the growth promotion hormones at issue?

Dr. Boisseau

123. In assessing the risk for human health associated with the exposure to veterinary drug residues, JECFA adresses the scientific uncertainty by using the safety factors listed above in my reply to question 8 describing, among others, how JECFA builds a margin of safety into its final recommendations.

124. For the hormonal growth promoters, JECFA has considered that, given the quality and the quantity of the available data, it was possible to carry out a complete quantitative risk assessment. For establishing ADIs and MRLs for the three synthetic hormones, melengestrol, trenbolone and zeranol, JECFA has implemented the usual procedure regarding the safety factors. For the three natural hormones, oestradiol-17β, progesterone and testosterone, JECFA has decided that the margin of safety deriving from the values of the established ADIs and from a maximum estimated intake of residue was such that it was not necessary to set up MRLs.

125. For oestradiol-17β, the European Communities did not consider any scientific uncertainty as it decided that it was not possible, for reasons of principle, to establish an ADI for a genotoxic compound. For the five other hormones at issue, the European Communities did not really consider any scientific uncertainty as it decided that the available data were too limited to allow a complete quantitative risk assessment to be carried out.

Dr. Boobis

Addressing scientific uncertainty in risk assessment

126. Scientific uncertainty is dealt with in a variety of ways in risk assessment. A description of some of the issues can be found in the draft report of the UK VUT (Variability and Uncertainty in Toxicology) working group of the COT (April, 2006) at *http://www.food.gov.uk/multimedia/pdfs/vutdraftreport.pdf.*

127. One way of dealing with uncertainty is to default to the worst case in the absence of evidence to the contrary. Hence, the most sensitive relevant endpoint in the most sensitive species is used as the basis of the risk assessment. In extrapolating to humans a default factor of 10 is used to allow for species differences, which assumes that humans are more sensitive than the experimental species. A further factor of 10 is included for interindividual differences. These differences may be due to gender, genetics, life stage or other factors. However, to some extent such differences have already been taken into account in the choice of endpoint, as this will usually represent the most sensitive lifestage, gender and to some extent genetics by using data from the most sensitive species. Where there are additional uncertainties, such as no NOEAL or the absence of a non-critical study, an additional safety factor will be included, and this is almost always conservative, as when the data gaps have been completed, the appropriate safety factor is almost always less than that used to account for these data gaps. The residue may be assumed to be all as active as the most active moiety, which is almost always a conservative assumption. Dietary intake is based on conservative data for food consumption. It is also assumed that all meat that could contain veterinary drug residue will contain the residue and that this will be present at the high end of the range (MRL or other appropriate level). In respect of the ADI, the assumption is that intake will be at this high level for a lifetime, when in reality there will be occasions when little or no meat is consumed or that which is consumed contains less or even no residue. In their risk assessment of the hormones, JECFA applied all of these approaches to dealing with the uncertainty.

128. In dealing with scientific uncertainty much depends on the expert judgment of the risk assessor. Issues such as biological coherence, whether effects are considered compound related, relevance to humans, the reliability of model systems at predicting effects in vivo all impact on the interpretation of the data. Within the EU, it is clear that there are also differences in the interpretation of data, as illustrated by the differing conclusions of the Committee on Veterinary and Medicinal Products - CVMP (1999) and the Scientific Committee on Veterinary Measures relating to Public Health - SCVPH (1999). In part, the EC assessment of the hormones did not go as far as including some of the considerations for uncertainty used by JECFA because of the conclusion that there was insufficient information to determine whether there was a threshold for the carcinogenic effects. However, for some of the compounds this was based on the results of a small number of non-standard tests of genotoxicity, with equivocal of very weak responses. It is not clear whether the EC applied a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking into account the totality of the available data, as was the case by JECFA.

CVMP (1999). Report of the CVMP on the Safety Evaluation of Steroidal Sex Hormones in particular for 17β-Oestradiol, Progesterone, Altrenogest, Flugestone acetate and Norgestomet in the Light of New Data/Information made available by the European Commission. EMEA/CVMP/885/99 (http://www.emea.eu.int/pdfs/vet/srwp/088599en.pdf)

SCVPH (1999). Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health: Assessment of potential risks to human health from hormone residues in bovine meat and meat products (http://ec.europa.eu/food/fs/sc/scv/out21_en.pdf)

C. ASSESSMENT OF OESTRADIOL-17B

13. To what extent, in your view, does the EC risk assessment identify the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol-17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice? To what extent does the EC risk assessment evaluate the potential occurrence of these adverse effects?

Dr. Boisseau

A. CARCINOGENIC POTENTIAL OF THE RESIDUES OF OESTRADIOL-17β

129. There is a general international agreement to recognize that oestradiol-17β is associated with a carcinogenic potential resulting from its interaction with hormonal receptors.

130. For exemple, in its fifty second session held in 1999, JECFA noted that "in long term studies in carcinogenicity in animals, reviewed at its thirty second meeting, oral and parenteral administration of oestradiol-17β increased the incidence of tumors only in hormone dependent tissues including the kidney of male Syrian hamsters" and concluded that "the carcinogenicity of oestradiol-17β is most probably a result of its interaction with hormonal receptors". Considering also epidemiological studies on women who took oestrogens, either alone or in combination with progestogens and androgens, JECFA concluded that " the available data suggest that the increase of cancers of the breast and the endometrium observed in women receiving post menopausal oestrogen replacement therapy is due to the hormonal effect of oestrogens. Therefore, JECFA has considered appropriate to establish a NOAEL on the basis of the changes in several hormone dependent parameters in post menopausal women and to derive from this NOAEL an ADI using two safety factors of 10, one to account for normal variation among individuals and a second one to protect the sensitive human populations.

131. In its 1999 report, CVMP concluded also that "hormonal carcinogens in humans and experimental animals are characterized by (1) tumorigenic action typically in various endocrine-responsive organs and/or tissues and (2) the need for a prolonged exposure to high concentrations before tumorigenic effects become apparent".

132. In its 1999 report, SCVPH concluded also that "whether it is clear that exogenous oestrogens, present in oral contraceptives or used in hormonal replacement therapy in women, are responsible for an increase risk of endometrial cancer and, to lesser extent, some increased risk of breast cancer, there is no direct evidence on the consequences of the contribution of exogenous oestradiol-17β originating from the consumption of treated meat".

B. GENOTOXIC POTENTIAL OF THE RESIDUES OF OESTRADIOL-17β

133. The amounts of substance needed to be used in toxicological studies in general are, by far, higher than the levels of residues likely to be present in food derived from animals treated by veterinary drugs. If these studies would have been carried out with the very little amounts of substances such as those corresponding to the residue levels in food, they would have always led to negative results. That is the reason for which these studies are, practically, always carried out with the parent substances and not with the residues and it is assumed that the residues derived from the parent substances have the same toxicological potential as these parent substances. As far as they are concerned, genotoxicity tests are mainly carried out in order to understand the mecanism of the carcinogenic effects, if any, of the substance under review and even the in vivo tests, because it is obvious for the in vitro studies, are not scheduled to determine a dose-response relationship and to

establish a threshold. Therefore, when genotoxicity tests give positive results, it is only possible to conclude that the parent substance itself has been shown genotoxic in the conditions of these tests and that its residues, given their very low levels in animal derived food, may have also a genotoxic potential.

134. There is currently some general agreement on the fact that oestradiol-17β is associated with a genotoxic effect.

135. Thus, although it recognized that oestradiol-17β does not lead to positive results in all the classical tests which have been used to demonstrate its genotoxicity and its mutagenicity (oestradiol-17β did not cause gene mutations in vitro and gives, in some other assays, sporadic but unconfirmed positive results), JECFA, in its fifty second session held in 1999, concluded "that oestradiol-17β has a genotoxic potential".

136. In its 1999 report, the Committee for Veterinary Medicinal Products (CVMP) of the European Medicine Agency (EMEA) released the following conclusions: "oestradiols and/or their synthetic analogues are devoid of the ability to induce gene mutations or chromosomes aberrations in vitro. With regard to the studies of Rajah and Pento (1995) and Thibodeau et al. (1998), those are considered inconclusive and, therefore, additional experiments are needed before making any statement that oestradiol-17β induces MTX resistance and/or HPRT-deficient gene mutations. Tsutsui and Barret and Tsutsui et al. hypothesised that oestradiols are capable of inducing aneuploidy, followed by malignant transformation and the studies of Abul-Hajj et al., Paquette, and Anderson et al. may suggest that oestradiol-17β and/or its metabolites induce DNA damage or genomic instability. However, the demonstration remains to be made that the observed indicator effects are representative of mutagenesis at the gene or chromosome level and also occur in somatic cells in vivo. This is not likely in the view of the following: earlier studies had mostly indicated that hormones do not induce micronuclei or other chromosomes aberration types in vivo. With the exception of the study reported by Dhilon and Dhillon, the recent data confirm the earlier findings and clearly indicate that hormones and/or their synthetic analogues are not associated with genotoxicity properties in the bone marrow micronucleus assay in vivo.

137. The sub-group of the UK Veterinary Product Committee (VPC) concluded in its 1999 report that "there is currently no positive results from internationally acccepted test systems which indicate that the hormones considered in the report are genotoxic".

138. In its 2002 opinion, SVCPH reported a series of new assays in which oestradiol-17β and/or its metabolites induce positive results but it has to be noted that all these assays have been carried out in vitro studies with cell cultures and no one in an in vivo study.

139. If there is currently some general agreement on the fact that oestradiol-17β is associated with a genotoxic effect, there is nevertheless no agreement on the fact that this genotoxic potential could be expressed in vivo in order to give to oestradiol-17β the capacity to act as a complete carcinogen, responsible of both initiation and promotion of tumours.

140. CVMP, quoting JECFA(1999) and IARC(1999) concluded that the potential genotoxic properties of the compounds(hormones and in particular oestradiol-17β) would not be expressed in vivo and/or not play a role in the tumorigenic activity. Therefore, it does mean that, even it has been considered that oestradiol-17β has a genotoxic potential, the tumorigenic activity of this hormone is not associated with its genotoxic potential but with its hormonal activity.

141. If SCVPH, in its 1999 report, expresses its concern in concluding that "Finally, in consideration of the recent data on the formation of genotoxic metabolites of oestradiol suggesting oestradiol-17β acts as complete carcinogen by exerting tumour initiating and promoting effects … no

quantitative estimate of the risk related to residues in meat could be presented", it provides no data indicating that oestradiol-17β is associated with the increase of tumours in tissues or organs which are not hormone dependent.

142. In conclusion, the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans.

C. OTHER ADVERSE EFFECTS ON HUMAN HEALTH

143. In its 1999 Opinion, SCVPH has also identified that hormonally active substances could be associated with other adverse effects concerning, for example, the intrauterine and perinatal development, the growth and puberty in humans and the immune system. Nevertheless, these data have not been used by the European Communities to conduct any quantitative risk assessment likely to lead, for these effects associated with the hormonal properties of growth promoters, to the establishment of thresholds and ADIs different from those proposed by JECFA.

Dr. Boobis

EC risk assessment of hormone residues in meat

144. The EC has not identified the potential for adverse effects on human health of residues of oestradiol found in meat from treated cattle. This is because the analysis undertaken was focused primarily on hazard identification. There was little in the way of hazard characterization, and no independent exposure assessment was undertaken. Data from the JECFA evaluation were used, together with speculative assumptions about misuse or abuse of the product. No adequate assessment of exposure following use according to GVP was undertaken. Hence, it was not possible to complete the risk characterization phase of the assessment. The EC's evaluation essentially stopped once it was concluded that the effects of the hormone were such that there were no thresholds (genotoxic carcinogenicity and hormonal effects). There was no attempt to estimate the potential occurrence of adverse effects in humans following exposure to levels of the hormones found in meat from treated animals.

Dr. Guttenplan

145. I believe the EC has done a thorough job in identifying the potential for adverse effects on human health of oestradiol-17β found in meat derived from cattle to which this hormone had been administered. They have identified a number of potential adverse effects of oestradiol-17β in humans. They have established metabolic pathways relevant to these effects, and have examined mechanisms of these effects. In addition they have performed thorough studies of residue levels in cattle, and the environment. The evidence evaluating the occurrence of adverse effects is weak. Animal models are very limited and the target organs do not coincide well with the target organs in humans. There are basically no epidemiological studies comparing matched populations consuming meat from untreated and hormone-treated cattle. Thus, little can be inferred about the potential occurrence of the adverse effects, the potential for adverse effects seems reasonable. (JECFA Meeting 52-WHO-FAS 43, SCVPH Opinions 1999, 2002).

14. In your view, does the risk assessment undertaken by the European Communities on oestradiol-17β follow the Codex Guidelines on risk assessment, including the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization with respect to oestradiol-17β?

Dr. Boisseau

146. The European Communities does not indicate anywhere in its submission that it does not intend to follow the Codex guidelines on risk assessment including the four steps of hazard identification, hazard characterisation, exposure assessment and risk characterisation. On the contrary,the following indicates that the European Communities considers the same approach for assessing the risk associated with the residues of growth promoters. It only claims, on the basis of the opinion released by the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) in 1999, as the two following opinions of this SCVPH, released successively in 2000 and 2002, did not amend this conclusion adopted in 1999, that it is not possible to carry out a quantitative risk assessment with regard to the six hormones in general and to oestradiol-17β in particular. For the European Communities, such a quantitative risk assessment cannot be carried out because "In consideration of the recent concerns relating to the lack of understanding of critical developmental periods in human life as well as the uncertainties in the estimates of endogenous hormone production rates and metabolic clearance capacity, in particular in prepubertal children, no threshold and therefore no ADI can be established for any of the six hormones".

147. After re-appraisal of 17 studies launched early in 1998 and recent literature, SCVPH, in its opinion released in 2002, adopted conclusions which do not challenge the Codex guidelines on risk assessment. SCVPH concluded, among others, that (1) "the consequence of the consumption of lipoidal esters of oestradiol-17β needs to be considered in a risk assessment", (2) "experiments with heifers, one of the major target animal groups for the use of hormones, indicated a dose dependent increase in residue levels of all hormones, particularly at the implantation site", "Epidemiological studies with opposite-sexed twins suggest that the exposure of the female co-twin in utero to hormones results in an increased birth weight and, consequently, an increase adult breast cancer risk" (These two statements call for refining the exposure assessment to hormone residues).

Dr. Boobis

Adherence of EC assessment to Codex risk assessment guidelines

148. As indicated above, the EC risk assessment of oestradiol does not follow the four steps of the Codex risk assessment paradigm. Even if it were concluded that oestradiol is a genotoxic carcinogen, the four steps should have been followed, for the reasons explained in answer to question 11 above, and as described further in the next section.

Dr. Guttenplan

149. The EC has been thorough in following Codex guidelines on hazard identification and very thorough in exposure assessment. The hazard characterization is more limited since there is only one animal model that is well characterized and this is in the hamster kidney. As kidney is not a known target of estradiol in humans the extrapolation to humans is uncertain. The risk characterization is very qualitative at best. There is also a mouse uterus model, but this has not been characterized with respect to dose-response and mechanism. More limited data is available in certain other animal systems and these are older studies with no reports of replication. There are no epidemiological studies comparing cancer incidence or prevalence in populations consuming hormone-treated or untreated meat, and, as indicated above, the hazard characterization is limited. Thus, taken together, the risk assessment has a mixed rating in following the Codex guidelines.

[The references for the two questions above are: para. 77 of EC Replies to Panel Questions and the Opinions in Exhibits US-1, 4, and 17; paras. 194-207 of EC Rebuttal Submission (US case), paras. 115-127 of EC Rebuttal Submission (Canada case), paras. 85-91, 134-153 of EC Replies to Panel Questions; paras. 35-40 US Rebuttal Submission, paras. 72-73 of US Replies to Panel

Questions, paras. 140-160 of US First Submission; paras. 70-111 of Canada Rebuttal Submission and paras. 88-106 of Canada First Submission]

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

15. Does the identification of oestradiol-17β as a human carcinogen indicate that there are potential adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes? Does your answer depend on whether good veterinary practices are followed? [see paras. 206-207 of EC Rebuttal Submission (US case), para. 121 of EC Rebuttal Submission (Canada case), para. 97-98 of EC Replies to Panel Questions, paras. 76-77, 150 and 155-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission]

Dr. Boisseau

150. Considering my reply to question 13, it is legitimate to conclude that (1) the carcinogenic potential of oestradiol-17β results from its hormonal activity, (2) it is possible to establish a NOAEL and, by using an appropriate safety factor, to derive from this NOAEL an ADI which represents the highest quantity of oestradiol-17β causing in humans no hormonal effect and therefore no carcinogenic effect. On these grounds, it is possible to conclude, in agreement with JECFA, that oestradiol-17β, even it has been recognized as being able to generate tumours, is not likely to produce adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes.

151. My reply depends on the efficient implementation of good veterinary practices. It has to be clearly understood that if these good veterinary practices are not implemented or if the conditions of use of the veterinary drugs in animal husbandry are different from those which have been taken into consideration by JECFA in its risk assessments, all the work carried out since years by both JECFA and Codex to establish MRLs to guarantee the hygienic quality of animal derived food and to protect human health with regard to veterinary drug residues is meaningless.

Dr. Boobis

Relevance of carcinogenicity of oestradiol-17β

152. The entire basis of risk assessment is based on the fact that there is a relationship between dose and effect. This is true even for compounds for which there is no threshold in their dose-response curve. Hence, the greater the dose the greater the risk. The corollary is that the lower the dose, the lower the risk. A key consideration in the risk assessment is whether there is a threshold in the dose-response. If not, whilst risk declines with dose, it does not reach zero until there is no exposure (zero dose). However, in the case of oestradiol, the issue is complicated by the fact that the compound is produced naturally in the body. Hence, an additional factor in the risk assessment of this compound is whether the levels from consumption of meat from treated animals impacts on the circulating levels of the hormone. If not, then there should be no change in risk.

153. JECFA concluded that whilst oestradiol is a human carcinogen, its mode of action is such that there would be no appreciable risk of cancer at exposures up to the ADI. The risk of cancer at exposures above the ADI would depend on the duration of exposure, which would need to be relatively prolonged (in the order of years rather than months) and on the magnitude of the exposure. It is likely that at exposures slightly above the ADI, the risk would be minimal. However, it is not possible to estimate with any accuracy at which level of exposure risk would become significant.

This would also vary with the individual. Exposure from meat of cattle treated according to GVP would be substantially below the ADI and hence the threshold for any carcinogenic effects. If GVP is not followed, then whether there is a carcinogenic risk would depend on whether the ADI is exceeded and by what margin. However, even if the ADI is exceeded, this would have to be on a regular basis. As indicated above, the occasional exposure above the ADI, such as might occur if GVP is not followed, would not be associated with any increase in risk of cancer.

Dr. Cogliano

154. The identification of oestradiol-17β as a human carcinogen indicates that there are potential adverse effects on human health when oestrodiol-17β is consumed in meat from cattle treated with hormones for growth promotion purposes. This answer does not depend on whether good veterinary practices are followed. It depends on the presence of the hormone in the meat that people consume.

Dr. Guttenplan

155. If potential is taken to mean possible, then an adverse effect cannot be ruled out, but it is unlikely if good veterinary practices are followed. If good veterinary practices are not followed, the potential for adverse effects may be significant. (JECFA Meeting 52-WHO-FAS 43, SCVPH Opinions 1999, 2002).

16. Does the scientific evidence relied upon in the SCVPH Opinions support the conclusion that carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity? [see para. 148 of the EC Replies to Panel Questions and paras. 35-40 and 46 of US Rebuttal Submission]

Dr. Boisseau

A. OESTRADIOL-17β

156. Considering my reply to the question 13, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity.

B. PROGESTERONE

157. In its thirty second session, JECFA concluded that "Although equivocal results have been reported for the induction of single-strand DNA breaks and DNA adducts have been seen in vivo and in vitro in some studies, progesterone was not mutagenic … progesterone has no genotoxic potential". It concluded also that "these effects on tumour production occurred only with doses of progesterone causing obvious hormonal effects … the effects of progesterone on tumour production was directly related to its hormonal activity".

158. In its 1999 report, SCVPH concluded, about the carcinogenicity of progesterone, that "At present, the data are insufficient to make any quantitative estimate of the risk arising from the exposure to residues in meat" Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of progesterone are related to a mechanism other than hormonal activity.

C. TESTOSTERONE

159. In its thirty second session, JECFA concluded that the increase of the incidence of prostactic and uterine tumours observed in rodents treated with high doses of testosterone resulted from the

hormonal activity of testosterone". In its fifty second session held in 1999, JECFA concluded that "In mammalian cells, no chromosomal aberrations, mutations or DNA adducts were found following treatment with testosterone … testosterone has no genotoxic potential".

160. In its 1999 report, SCVPH concluded, about the carcinogenicity of testosterone, that, given the limited data on genotoxicity and on carcinogenicity in humans, no conclusive quantitative estimate of the risk arising from the excess intake with meat from treated animals can be made. Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of testosterone are related to a mechanism other than hormonal activity.

D. MELENGESTROL

161. In its fifty fourth session, JECFA concluded from the review of a range of assays in vitro and in vivo that melengestrol acetate is not genotoxic. It also agreed upon the fact that "no firm conclusion could be drawn about the carcinogenic potential of melengestrol acetate in ICR mice … the increased incidence of malignant tumors in the highest-dose group of prepuberal C3Han/f mice was assumed to be due not to a direct carcinogenic effect of melengestrol acetate but to the promoting effect of increased prolactin concentrations".

162. In its 1999 report, SCVPH concluded, about the carcinogenicity of melengestrol, that "in view of the lack of data on mutagenicity/carcinogenicity and on DNA interactions and in consideration of carcinogenicity studies conducted only in one animal species, these data are inadequate to assess the carcinogenic potential of melengestrol. Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of melengestrol are related to a mechanism other than hormonal activity.

E. TRENBOLONE

163. In its thirty second session held in 1987, JECFA concluded from carcinogenic studies in animals that "the liver hyperplasia and tumours in mice … and the slight increase in the incidence of islet-cell of the pancreas of rats arose as a consequence of the hormonal activity of trenbolone". In its thirty fourth session held in 1989, JECFA, having reviewed a comprehensive battery of short term tests, concluded that " it was unlikely that trenbolone acetate was genotoxic" and decided to confirm its previous conclusion to base the evaluation of trenbolone acetate and its metabolites on their no-hormonal-effect.

164. In its 1999 report, SCVPH concluded, about the carcinogenicity of trenbolone, that "in consideration of the lack of in vitro short term assays on mutagenicity and genotoxicity of other trenbolone metabolites other than α-trenbolone and in consideration of the equivocal results of the transformation assays and the in vivo studies, the available information is insuficient to complete a quantitative risk assessment". Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of trenbolone are related to a mechanism other than hormonal activity.

F. ZERANOL

165. In its thirty second session held in 1987, JECFA concluded that zeranol and its metabolites, zearalanone and taleranol, were not mutagenic in a number of tests in bacterial and mammalian systems even if it has noted that zeranol gives a positive result in the Rec-assay and taleranol gives a positive result in the test with Chinese hamster ovary cells in the absence of activation but a negative result with activation. After having reviewed the carcinogenicity studies in animals, JECFA concluded that " the tumorigenic effect of zeranol was associated with its oestrogenic properties".

166. In its 1999 report, SCVPH concluded, about the carcinogenicity of zeranol, that "in consideration of the lack of data on mutagenicity/genotoxicity and the clear evidence for an induction of liver adenomas and carcinomas in one animal species, no assessment of the possible carcinogenicity of zeranol can be made". Therefore, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of zeranol are related to a mechanism other than hormonal activity.

167. In conclusion, considering my reply to question 13 above, the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity. On the other hand, considering the conclusions of JECFA and the fact that SCVPH bases always its reservations on the lack of data more than on data establishing the genotoxicity and the capacity of the five other hormones (progesterone, testosterone, melengestrol, trenbolone and zeranol) to act as complete carcinogens, it can be said that the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of these five hormones are related to a mechanism other than hormonal activity.

Dr. Boobis

Mechanism of carcinogenicity of oestradiol-17β

168. There is no doubt that some of the hormones in dispute are genotoxic and mutagenic in some assays *in vitro*. However, the conduct and interpretation of these assays requires expert judgment. Some endpoints are prone to artefactual positives, for example due to cytotoxicity and even a true positive may be a reflection of the non-physiological conditions of the in vitro system *(Greenwood et al, 2004; Kirkland et al, 2005)*. Hence, the guidelines on genotoxicity testing require confirmation of an in vitro positive using an appropriate in vivo assay *(CVMP, 2004)*. An additional factor is the testing of metabolites or putative metabolites. In vitro it is possible to test these unopposed by detoxication or excretion processes. However, in vivo, it is often the situation that some metabolites are not formed in sufficiently high concentrations for a sufficient period of time to cause any genotoxicity. A key example is the formation of reactive oxygen species. Whilst this is an established mechanism for mutagenicity in vitro, there is very little evidence for such an effect in vivo (*Bianco et al, 2003; Brusick, 2005*). Further, there is a threshold for this mechanism, due to the efficiency of endogenous antioxidant systems *(Aria et al, 2006; Russo et al, 2004)*. This is because endogenous production of reactive oxygen species during intermediary metabolism is substantial, and hence efficient protective systems have evolved to maintain the integrity of the cells *(Russo et al, 2004)*. For these reasons, in vitro studies implicating metabolites in the mode of action of a carcinogen should be supported by mechanistic studies in vivo. In particular, evidence for the formation and genotoxic effects of such metabolites should be sought in vivo. Whilst there is adequate evidence that some of the hormones are genotoxic in some in vitro assays, there are data supporting mechanisms other than direct reactivity with DNA. The possibility of redox cycling of some metabolites, with the generation of reactive oxygen species that can give rise to 8-hydroxylation of guanine has been discussed above (see also *Yagi et al, 2001*). Redox cycling may give rise to adducts by other mechanisms, such as formation of aldehydes *(Lin et al, 2003)*. There are clear thresholds for these interactions (see above). The evidence is against any direct interaction of oestradiol or its metabolites with DNA *(Chen et al, 2005; Hurh et al, 2004; Huez et al, 2004)*. Oestradiol can cause genotoxicty by effects other than direct or indirect interaction with DNA. These include induction of micronuclei *(Fischer et al, 2001)* and promotion of DNA instability *(Stopper et al, 2003)*, both of which exhibit thresholds.

169. The carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity. Some of the evidence for this is the target tissues, which are hormonally responsive, the concordance of carcinogenic effect with oestrogenic potency, the absence of reliable evidence for genotoxicity, including DNA binding, in target tissues (see above). It is notable that specific antagonism of the

oestrogen receptor in women with drugs such as tamoxifen, markedly reduces the risk of oestrogen-related cancers, such as of the breast in those with high risk factors due to endocrine status *(Fisher et al, 2005)*. This suggests that the carcinogenic effects of oestradiol are mediated, to the extent that can be estimated from such studies, by activation of the oestrogen receptor. The importance of the oestrogen receptor (ERα) in the carcinogenic effects of oestradiol is reinforced by the results of experimental studies in genetically engineered mice *(Tilli et al, 2003)*.

170. As indicated above, the studies in which positive results were obtained for the genotoxicity of oestradiol and upon which the conclusions of the EC regarding mechanism were based, should have been evaluated on a weight of evidence basis. Several of the studies suffered from significant limitations and there were a number of well conducted studies on a variety of endpoints that should have been included in such an evaluation.

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Dr. Guttenplan

171. The SCVPH Opinions (SCVPH Opinions 1999, 2002) do indicate that a mechanism other than hormonal activity is possible, "In acknowledging the recent findings on the metabolism based genotoxicity of 17-ß oestradiol (see chapter 2.5 of the report) it has to be stated that the assumption that the carcinogenic potential is exclusively related to the hormonal activity is no longer valid." However, the US and Canada cite other reports indicating that genotoxic effects of estrogens are unlikely. It should also be noted that more recent reports support a role for a genotoxic mechanism by which hormones contribute to cancer (SCVPH Opinion, 2002).

17. Could you comment on Canada's statement that "the studies commissioned by the European Communities also failed to find evidence of "catechol metabolites" – that is the oestradiol metabolites identified as the source of the genotoxic potential – in meat from treated animals"? What would be the implication of an absence or presence of catechol metabolites? [see para. 102 of Canada Rebuttal submission, EC Exhibit 51A]

Dr. Boisseau

172. The Canada statement that " the studies commissioned by the European Communities also failed to find evidence of " catechol metabolites "in meat from treated animals" seems right if the study reported in the Exhibit EC-51A is considered. It is written in this report, page 15, that, in an in vivo metabolic study, "(1) the presence of methoxy-oestrogens that derive by catechol-O-methyltransferase activity from catechol oestrogens was demonstrated neither in liver nor in kidney… (2) Residues … are scarcely detectable 12 days after injection of oestradiol-17β, that could be explained by a fast turn over of metabolites covalently bound to macromolecules, if really present, which should be different from catechol oestrogens adducts in proteins ... (3) However, gluthathione

or glucuronide conjugates of catechol oestrogens could be present at very low concentrations in liver or kidney extracts and could correspond to sub-minor peaks we have isolated without being able to identify them due to the too low amounts we have purifed … Nevertheless, in urine of one steer, we have identified a glucuronic acid derivative of a methoxy-estrone as a minor metabolite, which demonstrates that catechol oestrogen biosynthesis activity is present although very weak…. (4) no trace of catechol oestrogen adducts could be detected at the same time in this fraction " page 16, that, in in vitro studies, "No metabolites coming from the catechol oestrogen biosynthesis could be isolated" page 18, that "metabolic studies performed in vivo …and in vitro …failed to demonstrate a significant aromatic hydroxylation activity that would lead to catechol oestrogen derived metabolites.

173. In conclusion, (1) it can be said that this study could not find evidence of metabolites coming from the catechol oestrogen biosynthesis. Nevertheless, it cannot be excuded that such catechol oestrogen biosynthesis may exist although being very weak, (2) if the amount of catechol metabolites would have been demonstrated as being significant, which is not the case, the genotoxic potential of these metabolites would have to be taken into consideration in assessing the genotoxicity potential of oestradiol-17β.

Dr. Boobis

Relevance of catechol metabolites

174. The analytical data certainly show that levels of catechol metabolites in meat from treated animals were below the limits of detection of the method. This is consistent with the rapid detoxication and elimination of these metabolites in vivo. The implications for the risk assessment of oestradiol would depend on the underlying assumptions for the carcinogenic effects of the compound. For the catechols to be significant it would be necessary for these to be responsible for the carcinogenic effects of oestradiol, it would be necessary for there to be no threshold for their effects and if there were it would be necessary for intake to exceed this threshold. Oestradiol is itself carcinogenic at high doses in human subjects. Hence, there is no need for exposure to preformed catechols for a carcinogenic effect If these are necessary for the carcinogenicity, sufficient can be formed in vivo. However, as indicated above, there is no good evidence implicating catechols in the carcinogenic effects of the hormones. Further, also as discussed above, any genotoxicity of these compounds due to redox cycling would be militated against by endogenous anti-oxidant systems. Hence, whilst the absence of detectable catechols in meat from treated animals is reassuring, even if they were detected at low levels, it would not impact on the risk assessment.

Dr. Cogliano

175. The presence of catechol metabolites would support the potential for adverse effects to occur. The absence of catechol metabolites could imply either (1) that detectable levels of catechol metabolites were not formed from the parent compound or (2) that some level of catechol metabolites was formed that the test methods were not sufficiently sensitive to detect it.

Dr. Guttenplan

176. It is true that only very small amounts of catechol metabolites were detected in meat from treated animals. However, significant levels of estradiol and estrone were detected. These can be metabolized in humans to catechols *(Rogan EG. Badawi AF. Devanesan PD. Meza JL. Edney JA. West WW. Higginbotham SM. Cavalieri EL. Relative imbalances in estrogen metabolism and conjugation in breast tissue of women with carcinoma: potential biomarkers of susceptibility to cancer. Carcinogenesis. 24(4):697-702, 2003).* In contrast to humans, cattle do not efficiently metabolize estradiol to catechols. The latter explains the very low levels of catechols in meat. Thus,

the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity.

18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol-17β is genotoxic. Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see paras. 118-119 of EC Rebuttal Submission (US case), paras. 123-124 of EC Rebuttal Submission (Canada case), paras. 87-91 and 153-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission, and paras. 90-97 of Canada Rebuttal Submission]

Dr. Boisseau

177. This issue regarding the genotoxic potential of oestradiol-17β has been already adressed in my reply to the question 13. In addition, I would like to comment the content the para 118 and 119 of the EC Rebuttal Submission (US case). It is true that JECFA, considering the outcome of its assessment, did not think necessary in 1988 to establish an ADI for the three natural hormones. Later on, not because JECFA has amended its assessment regarding these three hormones but in order to present in a more convincing way the outcome of its assessment, it decided, in its fifty second session held in 1999, to establish an ADI for each of the three natural hormones and to indicate that the estimated intake of residues accounts respectively for 2%-4% of the ADI for oestradiol-17β, 0,03% of the ADI for progesterone and 0,05% of the ADI for testosterone. On the other hand, taking into consideration my reply to the question number 8, it has to be reminded that this theoritical estimated intake of residues is all the more conservative that it disregards the very poor oral bioavailability of these hormones.

178. My reply would not have been different at the time of adoption of the EC Directive in September 2003.

Dr. Boobis

Genotoxicity of oestradiol-17β

179. This issue has been discussed in detail in response to question 15. To reiterate, whilst there are reliable studies demonstrating the genotoxicity of oestradiol in certain in vitro tests, the evidence is against any genotoxicity in vivo. Some, if not all, of the genotoxicity observed in vitro would be expected to exhibit a threshold, particularly that involving reactive oxygen species. My reply to this question would have been the same at the time of adoption of the EC Directive in September 2003.

Dr. Cogliano

180. The EC does demonstrate through scientific evidence that oestradiol-17β is genotoxic. The issue, though, is whether this genotoxicity would occur at levels found in meat residues. The EC's last argument (in paragraph 124 of the EC's Rebuttal Submission, Canada case) that oestradiol-17β is carcinogenic by a combination of both genotoxicity and cell proliferation is not contradicted by earlier arguments made by Canada and the US. On the other hand, it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans.

Dr. Guttenplan

181. There was scientific evidence cited by the EC in 2003 that oestradiol-17β is genotoxic, "17β oestradiol induces mutations in various cultured mammalian cells. The reactive metabolite,

oestradiol-3,4-quinone, also induces mutations in mouse skin *in vivo*. The catechol oestrogen-quinones form DNA adducts in cultured cells and in mouse skin" (footnote 82, Rebuttal Submission (US case). This evidence was stronger compared to previous reports. However the evidence now is much stronger. *(Rogan EG. Cavalieri EL. Estrogen metabolites, conjugates, and DNA adducts: possible biomarkers for risk of breast, prostate, and other human cancers. Advances in Clinical Chemistry. 38:135-49, 2004.)*

19. The European Communities states that "... it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance". Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case), paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]

Dr. Boisseau

182. The issue regarding the genotoxic potential of oestradiol-17β has been already adressed in my reply to the question 13. The statement of the European Communities according which "it is generally recognized … is not of relevance" is correct as long as it refers to the assessment of residues of xenobiotics. The scientific evidence referred to by the European Communities does not demonstrate that this statement can also apply in the case of oestradiol-17β, progesterone and testosterone as these three natural hormones are produced by both humans and food producing animals. Therefore, even in the absence of any consumption of food coming from animals treated by growth promoting hormones, humans are naturally and continuously exposed to these natural hormones through, among others, (1) their own production of these hormones which may be very high, for exemple in the case of pregnant women, (2) the consumption of meat from non treated cattle, (3) the consumption of meat from other food producing animals, (4) the consumption of milk and eggs. To my knowledge, there is no epidemiological survey indicating that this continuous exposure of humans to these natural hormones results in any identified risk for health.

183. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Dr. Boobis

Genotoxic potential and the absence of a threshold

184. This issue has been addressed in part in responses above. Generally, in risk assessment within the EU and JECFA, for compounds that are carcinogenic by a genotoxic mechanism (or mode of action), it is assumed that there is no threshold and that there is no level below which exposure is considered without risk. Hence, in such circumstances no ADI would be set (as this would imply that there was a "safe" level). However, the important point here is that it is the carcinogenic effect that is of concern, not in vitro genotoxicity. Whilst in vivo genotoxicity without carcinogenicity may be of concern, carcinogenicity by a mode of action other than genotoxicity, for which there is a demonstrable and biologically plausible threshold, would not fall into this category. Hence, whilst oestradiol may be genotoxic in certain in vitro assays, whether this requires a no-threshold approach to risk assessment depends critically upon a) the mechanism for genotoxicity and b) the relevance of the in vitro findings for the in vivo effects. The EC has accepted that for some mechanisms of

genotoxicity, such as inhibition of spindle assembly, there is a threshold *(EC, 2005a)*. Redox active compounds also show a threshold in their genotoxic effects *(Brusick, 2005)*. In addition, the EC has accepted that on occasion kinetic factors in vivo may be such that the genotoxic potential of a compound that is positive in vitro is not expressed in vivo at normal exposure levels, and hence there is a de factor threshold (e.g. oral exposure to phenol; *European Chemicals Bureau, 2006)*. There is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this. Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance.

185. My reply to this question would have been the same at the time of adoption of the EC Directive in September 2003.

EC (2005a). Official Journal L 241 , 17/09/2005 P. 0051 – 0056

European Chemicals Bureau (2006). European Union Risk Assessment Report on phenol. CAS No. 108-95-2. EINECS No. 203-632-7. 1st Priority List, Volume 64. EUR 22229 EN

Dr. Cogliano

186. The EC's statement that a threshold cannot be identified reflects their view of genotoxic mechanisms, just as the contrary statement that there is a threshold and that this threshold is above the levels found in meat residues reflects how Canada and the US view genotoxic mechanisms. Neither statement has been demonstrated by the scientific evidence, rather, they are different assumptions that each party uses in their interpretation of the available evidence.

Dr. Guttenplan

187. The data referred to by the EC supports a genotoxic mechanism as well as a hormonal mechanism. It is true that there is no reason to expect a threshold to exist for a genotoxic chemical. Although DNA repair can occur, it presumably is occurring at all doses and the fraction of DNA damage repaired probably does not change at physiological levels, because the repair enzymes are unlikely to be saturated. The statement that, "the fact that doses used in growth promotion are low is not of relevance" is not necessarily true. (para. 118-119 of EC Rebuttal Submission (US case). For any toxin the dose determines the risk. When exposure is very low risk will be very low. However, one can argue about the definition of "low". It should also be noted that at very low levels of genotoxic carcinogens the decrease in risk is more than proportional than the decrease in applied dose.

188. The opinion about genotoxic effects would be less sure in 2003, but the opinion about the existence and significance of thresholds would not change.

20. In your view, how do the European Communities' conclusions above relate to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary"? To what extent, in your view, has JECFA's conclusion that oestradiol "has genotoxic potential" affected its recommendations on this hormone?

Dr. Boisseau

189. The European Communities' conclusions referred to in question 19 relate obviously to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary". The reply given to the question No 19 explains how it does and why these European Communities' conclusions are questionable.

190. The reply given to question 13 applies also to the second question of this question. JECFA's conclusions that oestradiol-17β "has genotoxic potential" did not affect its recommendations on this hormone.

Dr. Boobis

Relevance of endogenous occurrence of oestradiol-17β in its risk assessment

191. The EC's conclusions depend somewhat on the concept of incremental risk. This holds that whether an exogenous exposure is of concern depends on the magnitude of the underlying endogenous or background exposure. Some argue that for a compound with no threshold, even a very modest increment is of concern, whilst others would argue that a small percentage change would not materially affect risk (e.g. *ICRP, 2003)*. However, before considering the question of incremental risk, it is pertinent to ask whether low levels of exposure impact on circulating hormone levels at all. The production of oestradiol is under homeostatic control, that regulates its synthesis and degradation (reviewed by *Fotherby, 1996*). In addition, the bioavailability of orally ingested oestradiol is very low (<10%), due to presystemic metabolism (*Kuhnz et al, 1993)*. Hence, there should be a range of exposures for which there are compensatory alterations in endogenous levels, thereby maintaining the oestradiol level in the body. There is evidence that low exposures to oestradiol, though above those that are found in meat from treated animals, do not result in any measurable change in the circulating levels of oestradiol *(Mashchak et al, 1986).* Endogenous levels of oestradiol vary with physiological state. Hence, the endocrine effects of a given concentration of oestradiol will vary with the specific physiological state. As a consequence, a modest incremental increase in oestradiol concentration from exogenous exposure (above the ADI) might conceivably perturb endocrine effects, depending on the physiological state. However, non-endocrine effects, such as genotoxicity, will depend on the circulating concentration of oestradiol and will not vary with physiological state. Hence, the natural variations in circulating oestradiol levels should have a much greater effect on any genotoxic response than the much more modest change that could arise from the hormone in meat from treated animals, at any conceivable level arising from its use as a growth promoter. Indeed, this would be the case, regardless of the mechanism of carcinogenesis. Hence, the EC conclusions on the absence of safety at any level of exposure is somewhat at odds with the underlying basis of the Codex conclusion regarding the need for an ADI or MRL.

192. I do not believe that JECFA's conclusion that oestradiol has "genotoxic potential" affected its recommendations on this hormone, which were based on the conclusion that there was a threshold for its carcinogenic effects. JECFA's conclusion regarding genotoxicity was based on positive results in certain in vitro tests, but the evidence was against a mutagenic response in vivo.

*Fotherby K (1996). Bioavailability of orally administered sex steroids used in oral contraception and hormone replacement therapy. Contraception, **54**:59-69*

*ICRP (2003). The evolution of the system of radiological protection: the justification for the new ICRP recommendations. J Radiol Prot, **23**:129–142*

*Kuhnz W, Gansau C and Mahler M (1993). Pharmacokinetics of estradiol, free and total estrone, in young women following single intravenous and oral administration of 17 beta estradiol. Arzneimittelforschung (Drug Res), **9**:966-973*

*Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF and Mishell DR Jr (1986). Comparison of pharmacodynamic properties of various estrogen formulations. Am J Obstet Gynecol, **144**:511-518*

Dr. Cogliano

193. In my view, the EC's conclusions seem to reflect a concern that endogenous hormone levels are variable (the variability of endogenously produced hormone levels is recognized by Codex). In my view, the argument that the EC seems to be making is that a threshold cannot be established for the incremental human exposures that would be found in meat residues, because these additional exposures may not be safe for some parts of the population.

Dr. Guttenplan

194. The European Communities' conclusions above are at variance with those of Codex. Probably JECFA's conclusion that oestradiol "has genotoxic potential" had some effect on the European Communities' conclusions. However as also noted by the EC (SCVPH 2002 Opinion) newer methods of analyses have identified areas of concern, such as developmental effects, since levels of hormones in meat may represent a significant increase in endogenous levels of prepubescent children.

21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential? Does your answer depend on whether good veterinary practices are followed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see, *inter alia*, the SCVPH Opinions and paras. 63, 83, 89-91 and 93 of US First Submission, paras. 131-136 of Canada Rebuttal Submission]

Dr. Boisseau

195. My reply to question 16 applies also to the first question of this question.

196. The fact that good veterinary practices are followed or not has no impact on the genotoxic potential of these hormones.

197. My reply would not have been different at the time of adoption of the directive in September 2003.

Dr. Boobis

Genotoxicity of the five hormones other than oestradiol-17β

198. There is no evidence that the hormones testosterone or progesterone have genotoxic potential. There is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic. They were negative in a range of tests for genotoxicity. They were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. Trenbolone also produced a low level of DNA adducts measured by 32P-post-labelling *(Metzler and Pfeiffer, 2001)*. As indicated above, micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. In no case did any of the compounds produce a mutagenic response. These data are insufficient to support the conclusion that these hormones have genotoxic potential in vivo. Thus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo.

199. I would have replied the same to this question at the time of adoption of the EC Directive in September 2003.

*Metzler M and Pfeiffer E (2001). Genotoxic potential of xenobiotic growth promoters and their metabolites. APMIS, **109**:89-95*

Dr. Guttenplan

200. There is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential. There is some evidence that certain of the hormones have genotoxic potential, but generally the potential is weak. Testosterone and progesterone are negative in genotoxic assays. Zeranol can induce transformation of breast epithelial cells in culture with efficiency similar to that of estradiol, but the mechanism is not known, and it is negative or marginally active in other assays. Trenbolone is either negative or marginally active in *in vitro* genotoxic assays. MGA is negative in genotoxicity assays. Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice. My reply for the hormones would not have been different in September 2003 (SCVPH 2002 Opinion).

22. How would you define *in vivo* DNA repair mechanisms? How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat? Does your answer depend on whether good veterinary practices are followed in the administration of these hormones? To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones? Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why? [see paras. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission]

Dr. Boobis

DNA repair mechanisms

201. DNA repair mechanisms comprise a series of enzymatic systems that recognize different types of damage to DNA and repair it. There are different systems for different types of chemical modifier of DNA (e.g. small alkyl groups, bulky aromatic groups, oxidative damage), the site at which the damage occurs (e.g. O6 or N7 of guanine) and the nature of the damage (e.g. covalent modification, inter-strand cross-linking, single strand breaks) (reviewed in *Dip et al, 2004; Huffman et al, 2005; Sharova, 2005).* It has been estimated that endogenous processes are responsible for considerable oxidative DNA damage, but this rarely causes heritable changes to the cell *(Shigenaga et al, 1989; Pollycove and Feinendegen, 1999).* To a large extent this is because of the evolution of a flexible and very efficient DNA repair process. DNA damage caused by exogenous agents (genotoxins) is repaired by similar mechanisms. Hence, adduction of DNA is detectable at much lower doses that mutation *(Williams et al, 2004).* DNA repair capacity needs to be overwhelmed before mutagenicity increases as a linear function of dose, the lower end of the dose response showing non-linearity *(Williams et al, 2004).* A major difficulty in the risk assessment of such compounds however, is the identification of the threshold for such effects. This is because they occur with low incidence, and experimental studies do not have the statistical power to determine the location of the threshold with any confidence. Thus, whilst recognizing the likelihood for a threshold for even genotoxic effects *(Williams et al, 2004)*, the risk assessor if faced with the impossibility of locating it. The conservative solution is to assume that the response is linear and that there is no dose below which exposure is safe (e.g. *UK Committee on Carcinogenicity, 2004*).

202. As indicated above, the evidence is against direct modification of DNA in vivo by hormones in meat from treated animals, or by their metabolites produced in vivo. Indirect modification could conceivably come about by products of active oxygen. The DNA repair processes for this are amongst the most efficient *(Arai et al, 2006; Russo et al, 2004)* and even if such modification did occur, it is anticipated that no heritable change would result, because of DNA repair *(Arai et al, 2006)*. This would be true even at the levels of exposure that could arise should GVP not be followed.

203. My reply would have been the same at the time of adoption of the EC Directive in September 2003.

*Dip R, Camenisch U, Naegeli H (2004). Mechanisms of DNA damage recognition and strand discrimination in human nucleotide excision repair. DNA Repair (Amst), **3**:1409-1423*

*Huffman JL, Sundheim O, Tainer JA (2005). DNA base damage recognition and removal: new twists and grooves. Mutat Res, **577**:55-76*

*Sharova NP(2005). How does a cell repair damaged DNA? Biochemistry (Mosc), **70**:275-291*

*Shigenaga MK, Gimeno CJ, Ames BN (1989). Urinary 8-hydroxy-2'-deoxyguanosine as a biological marker of in vivo oxidative DNA damage. Proc Natl Acad Sci U S A, **86**:9697-9701*

*Pollycove M and Feinendegen LE (1999). Molecular biology, epidemiology, and the demise of the linear no-threshold (LNT) hypothesis. C R Acad Sci III, **322**:197-204*

UK Committee on Carcinogenicity (2004). Guidance on a Strategy for the Risk Assessment of Chemical Carcinogens, Department of Health, London (http://www.advisorybodies.doh.gov.uk/COC/guideline04.pdf)

*Williams GM, Iatropoulos MJ and Jeffrey AM (2004). Thresholds for the effects of 2-acetylaminofluorene in rat liver. Toxicol Pathol, **32,** Suppl 2:85-9.*

Dr. Guttenplan

How would you define *in vivo* DNA repair mechanisms?

204. DNA repair *in vivo* refers to the ability of the organism to remove damaged or chemically modified portions of DNA and replace them non-damaged DNA.

How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat?

205. The repair processes involved in DNA damage produced by estrogen metabolites are no different then those involved in DNA damage by many other DNA damaging agents. Most DNA damage by any agent is repaired and there is considerable redundancy is DNA repair, insuring that repair is effective. However, a small fraction of damage inevitably escapes repair. In essence, there is a race for repair and cell division. If cell division occurs before repair then a mutation or cell death may arise. Most DNA repair processes are not saturated in whole animals (including humans) as such high levels would likely accompany extremely toxic levels of carcinogens. Some DNA repair processes are faulty (error-prone). They enable the cell to survive potentially fatal DNA damage, but they increase the levels of mutations in the cell. Increased levels of mutations increase the risk of cancer. There is no reason to assume that DNA repair processes involved in DNA damage produced

by estrogen metabolites are any more or less effective than those involved in repair of other carcinogens.

Does your answer depend on whether good veterinary practices are followed in the administration of these hormones?

206. NO

To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones?

207. The scientific material referred to by the European Communities for the most part doesn't address DNA repair. However, since it is not likely to be different for estrogen derived damage than other types of damage it is not really relevant. There is some evidence referred to in the SCVPH Opinions that error-prone DNA repair of certain estrogen derived damage can occur.

Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why?

208. NO

Lindahl T. Wood RD. Quality control by DNA repair. Science. 286(5446):1897-905, 1999, para. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission.

23. To what extent is it necessary or possible to take into account the "long latency period" of cancer in the conduct of a risk assessment, which is supposed to assess carcinogenic effects of these hormones when consumed in meat? Have the hormones in dispute been used as growth promoters over a sufficient number of years for an assessment of their long-term effects on human health to be made? [see para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case)].

Dr. Boisseau

209. I don't think possible/useful to take into account the "long latency period" of cancer in order to assess properly and specifically the carcinogenic effects of residues of natural hormones only resulting from the treatment of food producing animals by growth promoting hormones. In my view, epidemiological studies carried out in humans during long enough in order to take into account this "long latency period" will not be able to discriminate, in the case of a possible but limited increase of tumours, between the responsabilities of (1) hormone residues resulting from the treatment of food producing animals by growth promoting hormones, (2) hormone residues resulting from the endogenous production of these animals, (3) other components of the diet including other food additives and contaminants. That is the reason for which, to my knowledge, even the hormones in dispute have already been used as growth promoters over a sufficient number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters.

Dr. Boobis

Latency period for cancer

210. The latency period is an important consideration in risk assessment, both in the design and in the interpretation of studies. Thus, the duration of exposure, either of experimental animals or in epidemiology studies, should be sufficiently long to permit assessment of effects with a long latency period. Most forms of cancer come into this category. The observational studies of humans (e.g. on HRT or oral contraceptives) and the experimental studies in animals covered a sufficiently long period to encompass the latency period for any carcinogenic effects of the hormones (see *IARC, 1999)*.

211. The long term studies of the hormones undertaken in experimental animals and in humans, involved much higher doses than would be encountered on consumption of meat from animals treated with growth promoting hormones. The maximum risk from such low levels of exposure, even assuming a linear dose-response relationship for cancer, would be such that it would be necessary to study extremely large populations to detect any increase in cancer incidence, particularly as the most likely cancers are quite common. This is because the lower the risk the greater the number of subjects that are required to detect it, a function of the power of the study which takes account the magnitude of the risk and the difference from the background rate *(Hunter, 1997)*. Hence, in the risk assessment of the hormones used as growth promoters, it is questionable whether an increase in risk, even if it existed, could be detected in exposed populations. However, it is still necessary to protect against such a risk. The risk assessment of the hormones conducted by JECFA suggested that there would be no risk at exposure levels up to the respective ADI. Even if duration of exposure were for a sufficiently long period (usually 20-25 years for solid tissue tumours), any increase in risk would probably not be detectable. Hence, a negative result from such an observational study would not resolve the issue.

212. A second issue with respect to the latency is the significance it has for interpretation of the exposure pattern. Where there is a long latency, and regular exposure is necessary before a carcinogenic response is manifest, as appears to be the case for the hormones in question *(Coombs et al, 2005)*, occasional exposures above the ADI will not pose any additional risk *(Larsen and Richold, 1999)*. Hence, latency is of value in assessing the risks from different exposure scenarios.

Coombs NJ, Taylor R, Wilcken N, Fiorica J and Boyages J (2005). Hormone replacement therapy and breast cancer risk in California. Breast J, 11:410-415

Hunter DJ (1997). Methodological issues in the use of biological markers in cancer epidemiology: cohort studies. IARC Sci Publ, 142:39-46

IARC (1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 72. Hormonal Contraception and Post-menopausal Hormonal Therapy, IARC, Lyon, France

Larsen JC and Richold M (199). Report of workshop on the significance of excursions of intake above the ADI. Regul Toxicol Pharmacol, 30:S2-12.

Dr. Cogliano

213. It is definitely necessary to take into account the latency period of cancer in the conduct of a risk assessment. In this regard, the guidelines for developing *IARC Monographs* state, "Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 year cannot provide

evidence for lack of carcinogenicity." [International Agency for Research on Cancer, Preamble to the *IARC Monographs*, http://monographs.iarc.fr]

Dr. Guttenplan

214. When epidemiological data is used in performing a risk assessment, the latency period is extremely important. Usually a latent period of 20 years is taken for cancer, but this varies with the carcinogen. It is indeed necessary to determine incidence or prevalence at different times after the onset of exposure. Attempting to perform a risk assessment based on epidemiological data obtained to soon after the onset of exposure can seriously underestimate risk. With respect to hormones in meat, it appears they have now been consumed for a sufficient number of years to observe strong or moderate increases in risk. However, if the risk increase is small, a large enough identifiable long-term exposed population may not be available.

Lagiou P. Trichopoulou A. Trichopoulos D. Nutritional epidemiology of cancer: accomplishments and prospects. [Lectures] Proceedings of the Nutrition Society. 61(2):217-22, 2002, para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case).

24. To what extent is it possible to identify possible co-founding factors causing cancer and attribute them to identified sources? What are the implications of these factors for the conduct of a risk assessment evaluating the adverse affects caused by residues of growth promoting hormones in meat? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

Dr. Boisseau

215. Generally, it is very difficult to identify possible co-founding factors causing cancer and attribute them to identified sources. The reply given to the question No 23 applies also to this question No 24.

216. My reply would not have been different at the time of adoption of the EC Directive in September 2003.

Dr. Boobis

Confounding factors in cancer attribution

217. Although the causes of many cancers remain to be identified (though they are likely to be multi-factorial), strong risk factors have been identified for a number of cancers. The main hormonally-related cancers are breast, ovarian and endometrium in women, testes and prostate in men *(IARC, 1999)*. In females, genetic factors, particularly *BRCA1* and *2*, have a strong influence on a small number of breast cancers (*Wooster and Weber, 2003)*. Breast and ovarian cancer are affected by a number of lifestyle factors, which in general influence circulating oestrogen levels *(Amant et al, 2005; Henderson and Feigelson, 2000; Vogel and Taioli, 2006)*. These include parity (number of children), age at first birth, age at menarche, menopausal state. In addition, there are associations with diet, such as fat and meat consumption, for male and female hormonally-related cancers *(Colli and Colli, 2006; Gonzalez, 2006; Kushi and Giovannucci, 2002; Rieck and Fiander, 2006; Shirai et al, 2002; Wakai etal, 2005)*. Exogenous exposure to high levels of hormones, such as oestradiol, can cause cancer *(JECFA, 2000b; IARC, 1999)*. However, though HRT (hormone replacement therapy) and oral contraceptive steroids (OCS) represent exposures orders of magnitude greater than those encountered in consuming meat from treated animals, the relative risk is still relatively modest (RR of 1.3 for oestrogen-only HRT *(Beral, 2003)*; RR of 1.24 in women taking combined OCS

(Collaborative Group on Hormonal Factors in Breast Cancer, 2006)). These risks were detectable only because of the very large populations involved.

218. A number of such factors could confound a study of the effects of growth promoting hormones in meat (they should not affect the risk assessment, but the interpretation of the data used in the risk assessment). For example, socioeconomic and demographic differences in lifestyle choices and diet may utterly confound exposure comparisons of growth promoting hormones in meat. Meat consumption, regardless of whether it is from animals treated with growth promoting hormones, is an independent risk factor for a number of hormonally-related cancers, including breast in females and prostate in males *(Colli and Colli, 2006*; *Gonzalez, 2006)*. The average age at first pregnancy, a lifestyle choice, is appreciable greater in some countries than in others *(Beets, 1999; United Nations Economic* Commission *for Europe, 2003)*, as is socioeconomic status *(Robert et al, 2004*. Thus any apparent effect of growth hormone exposure from meat of treated animals may be confounded by other known risk factors. Whilst it is sometimes possible to correct for confounding, when the risk from the confounder is appreciably greater than the risk from the exposure of interest, which is likely to be the situation here, it is very difficult to account for all of the confounding (for example, see *Toledano et al, 2005)*. Residual confounding may still bias the result, obscuring a null difference.

219. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E and Vergote I (2005). Endometrial cancer. Lancet, 366:491-505

Beets G (1999). Education and age at first birth. DEMOS, 15 (Special Issue)

Beral V (2003). Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet, 362:419-427. Erratum in: Lancet, 2003, 362:1160

Collaborative Group on Hormonal Factors in Breast Cancer (1996). Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet, 347:1713-1727

Colli JL and Colli A (2006). International comparisons of prostate cancer mortality rates with dietary practices and sunlight levels. Urol Oncol, 24:184-194

Gonzalez CA (2006). The European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr, 9:124-126.

Henderson BE and Feigelson HS (2000). Hormonal carcinogenesis. Carcinogenesis, 21:427-433

JECFA (2000b). Toxicological Evaluation of Certain Veterinary Drug Residues in Food: Who Food Additives Series 43, WHO, Geneva, Switzerland

Kushi L and Giovannucci E (2002). Dietary fat and cancer. Am J Med, 113, Suppl 9B:63S-70S

Rieck G and Fiander A (2006). The effect of lifestyle factors on gynaecological cancer. Best Pract Res Clin Obstet Gynaecol, 20:227-251

Robert SA, Strombom I, Trentham-Dietz A, Hampton JM, McElroy JA, Newcomb PA and Remington PL (2004). Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. Epidemiology, 15:442-450

Shirai T, Asamoto M, Takahashi S and Imaida K (2002). Diet and prostate cancer. Toxicology, 181-182:89-94.

Toledano MB, Nieuwenhuijsen MJ, Best N, Whitaker H, Hambly P, de Hoogh C, Fawell J, Jarup L and Elliott P (2005). Relation of trihalomethane concentrations in public water supplies to stillbirth and birth weight in three water regions in England. Environ Health Perspect, 113:225-232

United Nations Economic Commission for Europe (2003). Trends in Europe and North America

Vogel VG and Taioli E (2006). Have we found the ultimate risk factor for breast cancer? J Clin Oncol, 24:1791-1794

Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H and Tamakoshi A; JACC Study Group (2005). Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci, 96:590-599

Wooster R and Weber BL (2003), Breast and ovarian cancer, N Engl J Med 348:2339–2347

Dr. Cogliano

220. It is generally possible to identify confounding factors in epidemiological studies. [Please note that the question mentions "co-founding factors."] It is often difficult, however, to determine whether the observed tumours can be attributed to the agent under study or to a confounding factor. When a causal interpretation is credible but confounding factors cannot be ruled out, IARC considers this to provide *limited evidence of carcinogenicity*.

Dr. Guttenplan

221. Although the question mentions co-founding, from the documents submitted, what is probably meant is "confounding" factors. These are factors other than the one investigated which may also correlate with the disease endpoint. For instance, if meat eaters are also obese, the observed effects may result from obesity and not meat-eating (although the two may be related to each other). It would be very difficult to identify all of the confounders with meat eating and cancer, although there are many models for the effects of dietary agents on cancer incidence. One would want a perfectly matched group of consumers of hormone-treated meat with consumers of non-hormone-treated meat, where both groups have the same "lifestyle". This is probably difficult to achieve, since individuals consuming non-hormone-treated meat are probably very health conscious or from a different geographical region. A number of confounders can indeed be identified (e.g., age, race, sex, medications), but one is never sure if all or even most have been identified. These are important considerations for risk assessment of adverse affects caused by residues of growth promoting hormones in meat, as the effects of the hormones (if any) are likely to be small and might be obscured by confounders. The reply would not be different in 2003.

Potter JD. Colorectal cancer: molecules and populations. [Review] Journal of the National Cancer Institute. 91(11):916-32, 1999

25. To what extent do the three recent studies referred to by the European Communities confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones? Please also comment on the EC statement that one of the studies "was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, which means that the subjects should have been exposed to hormone-free meat in their diet. This may further imply that it cannot be excluded that the risk of cancer may be further increased if meat treated with hormones for animal growth promotion were to be consumed". [see paras. 145-148 of EC Rebuttal Submission (US case) and paras. 139-142 of EC Rebuttal Submission (Canada case), footnote 97 in para. 147 of EC Rebuttal Submission (US case), and Exhibits EC-71, 72, 73]

Dr. Boisseau

222. My comment concerning zeranol in the reply given to question 13 can apply to the first study about zeranol reported in this question 25.

223. My reply to question 23 can be used as the requested comment regarding the second study about colorectal cancer risk reported in this question 25.

224. Comments to be made on the EC statement that one of the studies " was carried out … to be consumed" can be derived from the very careful conclusions drawn by SCVPH in its 1999 report which say that " the link, if any, with consumption of hormone-treated meat cannot, at present, be confirmed nor refuted …there is moderately consistent evidence that higher meat consumption … is associated with higher risk of breast cancer … it was therefore concluded that diets high in meat possibly increase the risk of prostate cancer … there is a weakly consistent evidence that total meat consumption is associated with the risk of prostate cancer. For red meat, the evidence is moderately consistent". In conclusion, this EC statement just expresses a concern but does not provide any scientific evidence supporting this concern.

225. The third study about the treatment of postmenopausal women reported in this question No 25 is out of scope.

Dr. Boobis

The three recently published studies referred to by the EC (note that the relevant EC exhibits are EC-062, EC-071 and EC-072, respectively)

(a) Liu S and Lin YC (2004). Transformation of MCF-10A human breast epithelial cells by zeranol and oestradiol-17beta. Breast J, **10**:514-521.

226. This paper reports the effects of oestradiol-17β and zeranol on the breast cancer derived cell line MCF-10A. This cell line is devoid of ERα and has little or no ERβ. The data show that both compounds produced changes in the cells following multiple exposures that were characteristic of malignant transformation. However, it should be noted that the malignancy of the cells was not tested by inoculation into animals, which is the final evidence that complete transformation has occurred. The doses of the compounds used were high, particularly for the effects observed in MCF-7 (ERα positive) cells, in which the EC50 for proliferation is around 2 pM (cf LOEC of 15 nM in present study). There was no change in the response with concentration in the MCF-10A cells. There was no demonstration by the authors or by others of the metabolic capacity of the cells. The two compounds were equi-potent in both the ERα negative (MCF-10A) and ERα positive (MCF7) cells. This is somewhat surprising given the known difference in both oestrogenic (*Le Guevel and Pakdel, 2001)* and genotoxic *(Metzler and Pfeiffer, 2001; Stopper et al, 2003)* potency of the two compounds.

227. Nevertheless, the two compounds do appear to produce a positive response in the cells, which is consistent with previous studies in this cell line *(Russo et al, 2002)*. However, it is well established that oestrogens can be genotoxic in certain in vitro test systems, most likely a consequence of redox cycling with generation of reactive oxygen species. Evidence for this mechanism has been reported recently by *Cuendet et al (2004)*. As indicated above, genotoxicity by this mechanism should exhibit a threshold and is also militated against in vivo by antioxidant defence systems and efficient repair of oxidant-damaged DNA. Hence, the study by Liu and Lin (2004) does not confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones.

*Cuendet M, Liu X, Pisha E, Li Y, Yao J, Yu L and Bolton JL (2004). Equine estrogen metabolite 4-hydroxyequilenin induces anchorage-independent growth of human mammary epithelial MCF-10A cells: differential gene expression. Mutat Res, **550**:109-121*

*Le Guevel R and Pakdel F (2001). Assessment of oestrogenic potency of chemicals used as growth promoter by in-vitro methods. Hum Reprod, **16**:1030-1036*

*Russo J, Lareef MH, Tahin Q, Hu YF, Slater C, Ao X and Russo IH(2002). 17Beta-estradiol is carcinogenic in human breast epithelial cells. J Steroid Biochem Mol Biol, **80**):149-16.*

(b) Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjonneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Lund E, Skeie G, Ardanaz E, Gonzalez C, Navarro C, Quiros JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hemon B, Saracci R, Kaaks R and Riboli E (2005). Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst, **97**:906-916.

228. This paper reports the results of a prospective epidemiological study into the relationship between diet and colorectal cancer. The study, in a large number of subjects, confirms previous reports that there is a statistically significant association between the consumption of red meat and the risk of developing colorectal cancer. This association has been know for some time (for example see *Modan, 1977)*. Moreover, it is a relatively consistent observation, regardless of geographical area (subject to allowance for any confounding by known risk factors) *(Marques-Vidal et al, 2006)*. A number of possible explanations have been proposed for this association, including the formation of mutagens during the cooking of meat *(Sinha et al, 2005)* and the generation of nitroso compounds in the colon through the effects of heam iron from meat *(Cross et al, 2003)*. Although the geographical variation in risk is consistent with a role of meat consumption in coloreactal cancr, it provides little support for a contribution from hormones present in meat from their use as growth promoters. This is because the association is just as strong in regions where hormones are not used as where they are used. Age standardized rates for colorectal cancer in males and females are 48.2 and 36.9 in Australasia, 44.4 and 32.8 in North America, 37.5 and 26.4 in Northern Europe and 35.9 and 23.5 in Southern Europe *(IARC, GLOBOCAN 2002)*. In comparison, meat consumption as protein is as follows: Australia 40.3 g/day, USA 40.2 g/day and Europe 25.2 g/day (FAO, 2003).

229. Hence, the study by Norat et al (2005) does not confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones.

Cross AJ, Pollock JR, Bingham SA (2003). Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. Cancer Res, 63:2358-2360

FAO (2003). FAOSTAT (http://faostat.fao.org/)

IARC (2002). GLOBOCAN (http://www-dep.iarc.fr/)

Marques-Vidal P, Ravasco P and Ermelinda Camilo M (2006). Foodstuffs and colorectal cancer risk: a review. Clin Nutr, 25:14-36

Modan B (1977). Role of diet in cancer etiology. Cancer, 40 (4 Suppl):1887-1891

*Sinha R, Peters U, Cross AJ, Kulldorff M, Weissfeld JL, Pinsky PF, Rothman N and Hayes RB (2005). Meat, meat cooking methods and preservation, and risk for colorectal adenoma. Cancer Res, **65**:8034-8041*

(c) Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM and Ockene J; Writing Group for the Women's Health Initiative Investigators (2002). Risks and benefits of oestrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA, 288:321-333.

230. This paper reports the results of a randomised controlled trial on the use of a combination of oestrogen and progestin as hormone replacement therapy. The hazard ratio in the group receiving the hormones for breast cancer was 1.26 (95% CI: 1.00-1.59). There was a reduction in the risk of colorectal cancer (0.63; 0.43-0.92) and no change in the risk of endometrial cancer (0.83; 0.47-1.47). This study confirms a number of previous reports, that exposure of postmenopausal women to an oestrogen-progestin combination increases the risk of breast cancer (see above; *Beral, 2003*). This was recognised by JECFA in its risk assessment of these hormones (*JECFA, 2000b)*. However, whether the finding is relevant to the risk from residues of the hormones in meat due to their use as growth promoters depends upon the conclusions of the risk assessment. Hence, as explained above, the weight of evidence is such that the hormones cause cancer by a mechanism exhibiting a threshold. As long as exposure does not consistently exceed the ADI, there should be no appreciable risk to human health. Related to this, the doses to which the women receiving hormone replacement therapy were exposed in this study were many times those to which consumers would be exposed from meat from cattle treated with growth promoting hormones.

231. Hence, the study by Rossouw et al (2002) does not confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones.

232. With respect to the EC statement on the significance of the fact that one of the studies *(Norat et al, 2005)* was performed after a ban on the use of hormones for growth promotion in Europe, this will depend on the interpretation of the risk assessment. If there is no risk from the consumption of meat from animals treated with the hormones, as was the view of JECFA, then it would be immaterial whether the study was conducted before or after the ban, the risk would have been the same. If the risk is non-zero, as suggested by the EC, then certainly there might be an incrementally greater risk if such meat were consumed. However, as indicated elsewhere in my responses, the evidence is against an increased risk from such exposures. In addition, the EC statement is not scientifically defensible. The risk of cancer when eating meat from treated animals has not been measured. Hence, it is impossible to infer anything from the risk in the absence of such exposure. The EC could have made such a statement in the absence of any study as it is based entirely on conjecture.

Dr. Cogliano

233. The study by Norat et al (2005) indicates a risk to human health from the consumption of meat. The other two studies suggest a risk to human health (the term "suggest" is used rather than "indicate" because the exposure levels in these studies are higher than those found in meat residues). When a dietary study includes exposures to hormone-free meat, this would reduce the observed level of risk. As a result, the risk from exposure to meat containing hormones would likely be higher than what was indicated in the study.

Dr. Guttenplan

234. The first of the studies suggests a risk from zeranol. That observation was not previously reported. However, the results were obtained in cultured cells and the relevance to human exposure to hormone-treated cannot be extrapolated from this study because of a myriad of uncertainties in such extrapolation. The study does suggest that additional tests of zeranol should be carried out. There is also some evidence that a metabolite of zeranol (zearalenone) induces oxidative damage in cultured cells. This is a possible genotoxic effect, but again it cannot be extrapolated to meat consumption. The other two studies do not confirm a risk from hormone-treated meat. The statement that one of the studies was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, negates any relevance to the possible connection of hormone-treated meat consumption and cancer.

26. Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91]

Dr. Boisseau

235. My replies to questions 23 and 25 apply also to this question 26.

236. My reply would not have been different at the time of adoption of the directive in September 2003.

Dr. Boobis

Significance of epidemiological studies for risk from the hormones

237. Information relevant to this issue can be found in my responses to questions 24 and 25 above.

238. There is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans. There are some studies that are consistent with such an association, but there are several other possible explanations for the findings, some of which are more plausible than hormones in meat as being causal. In addition, there is some lack of consistency in the epidemiological studies between the associations observed and use of the growth promoting hormones.

239. There are an appreciable number of studies showing an association between the risk of certain cancer types, including breast and prostate and the consumption of meat *(Colli and Colli, 2006; Norat et al, 2005; see also SCVPH Opinion, 1999).* For breast, the incidence is similar is developed countries such as Western Europe, North America and Australasia. The correlation is strongest with meat consumption and shows little relationship with whether the meat is from animals treated with growth promoting hormones or not. For example rates in Iceland (87.2 per 100,000), where such hormones are not used, are not dissimilar to those in the USA (101.1 per 100,000), where they are used. Prostate cancer rates are 124.8/100,000 in the USA and 90.9 per 100,000 in Sweden *(IARC, 2002)*. For comparison, average daily consumption of meat (as protein) in 2000 was as follows: USA 40.2 g/day; Iceland 29.5 g/day; Sweden 24.8 g/day *(FAO, 2003).* Hence, there is a much better association with meat consumption and risk of breast or prostate cancer than there is with the use of growth promoting hormones to treat cattle. It is also important not to infer too much from geographical differences in cancer incidence rates with respect to causation. This is because of what is known as the ecological fallacy. This has been defined as the inference that a correlation between variables derived from data grouped in social or other aggregates (ecological units) will hold between persons (individual units) *(Society for Risk Assessment, 2004).* The difficulty is that many factors will vary between populations, including ethnicity, genetics, health and socioeconomic status, diet, lifestyle and environment. Without considering the possibility of confounding, such ecological data is really only of value in generating hypotheses *(Morgenstern, 1995).* These would need to be evaluated in more structured investigations, with better control of confounding variables.

Morgenstern H (1995). Ecologic studies in epidemiology: concepts, principles, and methods. Annu Rev Public Health, 16:61-81

Society for Risk Assessment (2004). Glossary of Risk Analysis Terms. (http://www.sra.org/resources_glossary.php)

240. My reply to this question would have been the same at the time of the adoption of EC Directive in September, 2003. Although some of the studies cited above were not published at that time, there was still sufficient information to identify the clear trend between meat consumption and the risk of breast and prostate cancer, independent of the pattern of use of the growth promoting hormones.

Dr. Cogliano

241. The difference between the US and the EC in rates of breast cancer and prostate cancer almost certainly has multiple causes. It is possible that differences in exposure to exogenous hormones can be one cause, but the data are not sufficiently specific to establish a link between these observations.

Dr. Guttenplan

242. The epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters. The references to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities are not very convincing as there is considerable variation in rates in different geographical locations. Also, the differences in rates of breast and prostate cancer observed in the United States as compared to the European Communities are relatively small. There is no way to definitely establish a link between these statistics and the consumption of meat from animals treated with the hormones at issue as there are many possible confounders, and the differences in cancer rates are small. However, the results are at least consistent with a possible effect of hormones on breast and prostate cancer. My reply would not have been different in 2003.

Pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91.

(b) Residue analysis

27. How do the residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue?

Dr. Boisseau

243. Residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue because the parent substances being different chemical entities associated with specific toxicological and physiological properties, the residues deriving from these different substances will be also different chemical entities associated with specific toxicological and physiological properties.

Dr. De Brabander

244. The residues of the three synthetic growth promoting hormones are substances which are exogenous: they do not occur in the body of a healthy human being or animal.

245. The structures of the synthetic hormones are different from those of the natural hormones. Melengestrol and trenbolone could be considered as being derived from respectively progesterone and testosterone while zeranol has a totally other structure.

28. How do the hormones naturally present in animals, meat, or human beings differ from the residues in meat of the three natural hormones used for growth promotion purposes?

Dr. Boisseau

246. The definition of residues encompasses both the parent substance and all the metabolites derived from this parent substance. Therefore, in the case of the part of residues of the natural hormones which consists of parent substances, there is no difference between hormones naturally present in food producing animals, meat or human beings. Metabolites of these natural hormones existing in cattle and meat are, obviously, the same. To my knowledge, there is no scientific evidence showing that the main metabolites of the three natural hormones existing in cattle and humans are not similar.

Dr. De Brabander

247. At first sight there are no differences between residues in meat of the three natural hormones used for growth promotion purposes and the hormones naturally present in animals, meat and human beings. However …

- The use of the three natural hormones used for growth promotion purposes will trigger a mechanism of reactions in the body of animals and human beings which may lead to the presence of other substances which **are not** naturally present. The conversion of testosterone to boldenone is an example. Boldenone is a very potent hormone used by "body-builders"

- The "natural" hormones used for growth promotion purposes are synthetised (prepared) from plant material. In plant material the $^{13}C/^{12}C$ ratio is different from the

$^{13}C/^{12}C$ ratio of animals. Research is ongoing which demonstrates that the pattern of hormones changes by the application of the "natural" hormones used for growth promotion purposes. (see further question 32)

- The residues of the natural hormones in cattle are in the 17α form (inactive) while the use of "natural" hormones used for growth promotion purposes may lead to residues in the ß form (active form)

- The residues of (the esters of) the natural hormones are incoporated in hair of the animals.

29. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the synthetic hormones found in meat in their assessment of the risks from such residues? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? How do they compare with the MRLs set by Codex? [see para. 165-176 of EC Rebuttal Submission (US case); pages 55-68 of the Opinion of the SCVPH of 30 April 1999 in US Exhibit 4, para. 144 of US First Submission, Exhibits US-6 and 7, footnote 46 of US Rebuttal Submission]

Dr. Boisseau

248. Levels of residues are taken into consideration at the third step, exposure assessment, of the risk assessment procedure after an ADI has been established at the end of the second step, hazard characterisation, of this procedure. As, in its 1999 report, SCVPH concluded "that no threshold level and, therefore, no ADI can be established for any of the six hormones" (including the three synthetic ones), there was no need for SCVPH to conduct a quantitative assessment of the exposure of consumers to the residues of hormonal growth promoters including the determination of the levels of residues in food from treated animals, the impact of the non observance of good veterinary practices on these levels and the comparison between these levels and the MRLs set up by Codex.

Dr. De Brabander

249. In the case of the 3 synthetic hormones the assessment of risk as evaluated by the SCVPH is in terms of actual residue levels is less complex than in the case of the natural hormones: since these hormones does not occur naturally the endogenous levels in humans and in the environment are to be considered as zero.

250. Each administration of these 3 hormones will increase the levels of these hormones in human causing a number of effects, cited by the SCVPH and leaving the doubt about a number of still unknown effects. Moreover, for the risk assessment some "old" data for residue concentrations are used.

251. In my experience, extreme care should be taken regarding publications of concentrations of residues. These concentrations cited (e.g. Table 8 : residue levels of alpha and beta trenbolone in tissues of treated cattle ; p 56 ; exhibit US-4) are extremely low (e.g. 10 ng/kg (= 10 ppt)) and serious doubts about their accuracy can be made. At the time they were produced (1987) there were no analytical methods available to quantify these residues at that concentration level in a correct way (methods as GC-MS-MS or LC-MS-MS). The detection capability and way of validation of analytical method have changed a lot in the last 20 years. The concentrations may seriously be underestimated making the risk assessment even more risky.

252. Moreover, all studies are too much focused on the direct effect on human health **only** (NOEL, ADI, MRL). As demonstrated in several documents a major part of the hormones used are excreted

through the faeces (for MGA ca. 75 %) from which they enter into the environment causing a number of uncontrolable effects. In the case of the 3 synthetic hormones there are no enough data on their metabolites, possible transition products and effects on the large number of aquatic life in our environment.

253. The MRLs set by the codex are high in relation to modern analytical limits (normally $\leq$ 1 µg/kg)

Trenbolone and zeranol	Cattle - Muscle -	2 µg/kg
	Cattle - Liver -	10 µg/kg
Melengestrol acetate	Cattle-liver	5 µg/kg
	Cattle-fat	8 µg/kg

254. Both from their relation to human health in all of its aspects and from an analytical point of view these MRLs are not acceptable.

30. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the three natural hormones in meat in their assessment of the risks from such residues? Is it possible to compare these to the ADIs recommended by JECFA in 1999? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? [see paras. 120-123 and 155-164 of EC Rebuttal Submission (US case), pages 33-54 of 1999 Opinion in Exhibit US-4, para. 144 of US First Submission, and 52nd JECFA Report in Exhibit US-5]

Dr. Boisseau

255. My reply to question 29 applies also to this question.

Dr. Boobis

Exposure assessment in the SCVPH Opinions

256. In the SCVPH Opinions of 1999 and 2002, the Committee did not itself evaluate evidence on the incurred residue levels of the three natural hormones in meat in their assessment of risks from such residues. In their 1999 Opinion, the Committee cited the data tabulated by JECFA but then calculated an exposure based on the US tolerances, which resulted in higher estimates of exposure than the theoretical maximum daily intakes (TMDIs) calculated on the basis of incurred residue levels by JECFA in 1999. In this Opinion, there is also some confusion between ADIs and tolerances (which are equivalent to MRLs). Tolerances are set to enable compliance to be determined. However, exposure at the tolerance level cannot be equated with risk to health. It is the ADI that determines whether there is a health risk at a given exposure. In their 2002 Opinion, the Committee did not revisit exposure following use according to GVP. Rather, the Committee considered potential exposure following several inappropriate use scenarios. This was based on a series of experimental studies, to determine the consequences of a number of defined misuses on hormone levels in meat. However, whilst of potential value in any risk assessment, these data are limited in the absence of any information on the frequency of occurrence of such misuse in the use of the products in question in normal veterinary practice. It would have been possible to compare the SCVPHs estimates of exposure with the ADIs derived by the JECFA but this was not done. The ADI would have exceeded the exposure estimates for the three hormones. In both Opinions, comparison was with estimated intake at the US tolerances.

257. References are provided to a series of studies on the effect of various misuse scenarios on residue levels. However, no references are provided that the effects GVP or the lack thereof has on residue levels in normal veterinary practice.

SCVPH (2002). Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health: Review of previous SCVPH opinions of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products (http://ec.europa.eu/food/fs/sc/scv/out50_en.pdf)

Dr. De Brabander

258. In the case of the three natural hormones the assessment of risk as evaluated by the SCVPH is in terms of actual residue levels and is more complicated than in the case of the synthetic hormones. Different data of concentrations of endogenous levels of the 3 hormones in humans and in farm animals could be found in literature.

259. The argument used in favour of the allowance of natural hormones is often that the contribution of the residues of these hormones in meat is only a small part of the naturally produced hormones in the body of a human being (JECFA,1987). Again, for the risk assessment some "old" data for residue concentrations are used and their accuracy could be doubted.

260. As for the three synthetic hormones, all studies are focused too much on the direct effect on human health only (as measured witt a NOEL, ADI, MRL etc.). As demonstrated in several studies a major part of the hormones used are excreted through urine and faeces and the administration of natural hormones to a herd increases the concentration of these hormones in the environment. Recently it was demonstrated in our laboratory that maggots of flies were able to convert high concentrations of natural hormones to strongly anabolic agents as boldenone and boldione

261. Moreover it should not be overlooked that these hormones may act as pheromones. The best known example is androstenone (the pheromone of the boar). But on Thursday, 10 February, 2005 BBC news mentioned that: a spray that helps increase women's enjoyment of sex has undergone successful trials. The spray, developed by Australian company Acrux, contains the male sex hormone testosterone. It was initially designed with post-menopausal women in mind, but has also been shown to work for young women with a low libido. The spray was tested over four months in three doses on 261 women with a low sex drive and low testosterone levels.

262. The tests with this type of spray illustrated the impact of hormones on human behaviour. Dr Geoff Hackett, of the British Society for Sexual Medicine, said it was important that the spray was only given to women who had been thoroughly assessed, and shown to have low testosterone. Dr Hackett also warned that raising testosterone levels too high was linked to side effects such as beard growth, hair loss, greasy skin and acne.

263. In addition to the above there is also ZMA (sold by a well known lab in the US and on the internet). ZMA is a scientifically designed anabolic mineral formula. It contains Zinc Monomethionine Aspartate plus Magnesium Aspartate and vitamin B-6, and is an all-natural product that has been clinically proven to significantly increase anabolic hormone levels and muscle strength in trained athletes. In tests the ZMA group had 30% increases in free and total testosterone levels compared to 10 percent decreases in the placebo group. The ZMA group also had a slight *increase* in insulin-like growth factor-1 (IGF-1) levels compared to a 20 percent *decrease* in the placebo group.

264. In all studies on residue levels of natural hormones I have found no indication of the influence of such ZMA formulations (and synergism with implantation). However, elements such as Zn and Mg are known to play an important role in enzymatic reactions.

31. Please comment on the US statement that "concentrations of oestradiol-17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of oestradiol-17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." In your reply please take into account the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels" and the statement by the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered. [see para. 51 and 144 of US First Submission and Exhibits US-6 and 7, para. 98 of EC Replies to Panel Questions, Exhibit EC-101, and para. 2.3.2.3 of the 1999 Report of SCVPH]

Dr. Boisseau

265. The US statement that " concentrations …naturally observed levels " is certainly right if one considers included among the physiological range of oestradiol-17β and of progesterone in cattle the levels of these hormones occurring during pregnancy. It is also true that meat and milk from non treated cattle contain residues of these two natural hormones. The comment of the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered " is also true. Even if, accepting the substance of the EC comment, it is possible to limit the physiological range of oestradiol-17β and of progesterone in cattle, it has nevertheless to be recognized that (1) consumers are exposed to these two natural hormones through their consumption of meat and milk from the different non treated food producing animals and, mainly as least for women, through their endogenous production, (2) this exposure cannot be avoided. Therefore, the use of the concept of threshold in the risk assessment of the natural hormone residues is legitimate and the additional intake of residues of these natural hormones from the meat from treated cattle has to be considered in this context and not according to a theoretical " no additional intake of residues is acceptable".

Dr. De Brabander

266. The US statement that "concentrations of oestradiol-17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle" may at first sight be correct. However, pregnant animals are normally not slaughtered and even if one is, the consumption of meat from those animals is small. On the contrary, if all animals are treated with estradiol-17ß there could be a significant increase of estradiol in human food. Meat and milk may contain estrogens (as also other foods which may contain estrogens but which don't pose problems at a normal food consumption level) and therefore there is no need to add more by artificial ways.

267. Moreover, the use of hormones is not only questioned from the point of view of the risk of food:

- There is also the influence on animal welfare, which is an important item. There are a lot of publications indicating that the use of hormones will influence behaviour in animals (and humans). Animals treated with hormones may become more aggressive or feel unconfortable. Nowadays this is not tolerated.

- There is the influence on the environment. All natural hormones as well as the synthetic ones end up in the environment. If the load of hormones is too high this may influence the life and behaviour of some fish and invertebrates and changing the normal pathway of life. There are a lot of investigations in that area

- Finally, most consumers in Europe don't want that the meat they eat is derived from animals treated with hormones (and want to also keep the level of veterinary drugs used as low as possible). This tendency of the consumer, increasing over the years is taken over by distribution chains who finally are deciding what is coming into the market.

32. Please comment on the conclusions of the EC risk assessment (Opinion of the SCVPH of April 2002) that ultra sensitive methods to detect residues of hormones in animal tissues have become available but need further validation. What is the significance of this with regard to identifying whether the natural hormones in meat are endogenously produced or are residues of hormones used for growth promotion purposes?

Dr. Boisseau

268. It is a general requirement that any analytical method, used to detect residues among others, be validated before being used. This validation must be carried out in compliance with well defined and internationally accepted criteria. As these ultrasensitive methods, referred to by the European Communities, are not yet properly validated, there is a need for additional work in this domain. Nevertheless, it has to be reminded that, when MRLs have been established for a given substance, there is not any more a need for highly sensitive analytical methods but for a validated analytical method the sensitivity of which must be consistent with the values of the established MRLs. In addition, if it is true that ultrasensitive analytical methods remain useful to control the use of forbidden veterinary drugs, such as for example growth promoters in EU, they are less useful in the case of the three natural hormones, which are endogenously produced by food producing animals.

Dr. De Brabander

269. Methods for the determination of hormones are improving constantly and it can be forseen that they will do so for some time. When I started -as a chemist- in the faculty of veterinary medicine (1973) the method of choice was TLC (Thin Layer Chromatography) with fluorescence detection. That method has been used (with succes) for some time untill GC-MS (gas chromatography with mass spectrometric detection) was coming up (in practice end of the 80's). Later MS-MS and even MS^n could be used as a very selective detector. In the middle of the 90's affordable LC-MS systems came on the market.

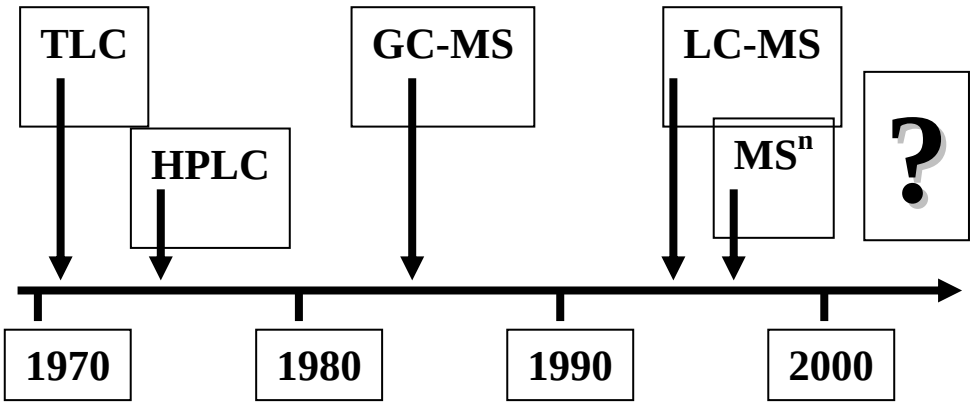

Fig 32.1: Evolution of the availability of analytical techniques in function of time.

270. LC-MS is still strongly in evolution. As an illustration Fig 32.2 shows the evolution of limits of detection of GC and LC-MS. As can be seen the LOD's has decreased considerably in the last years.

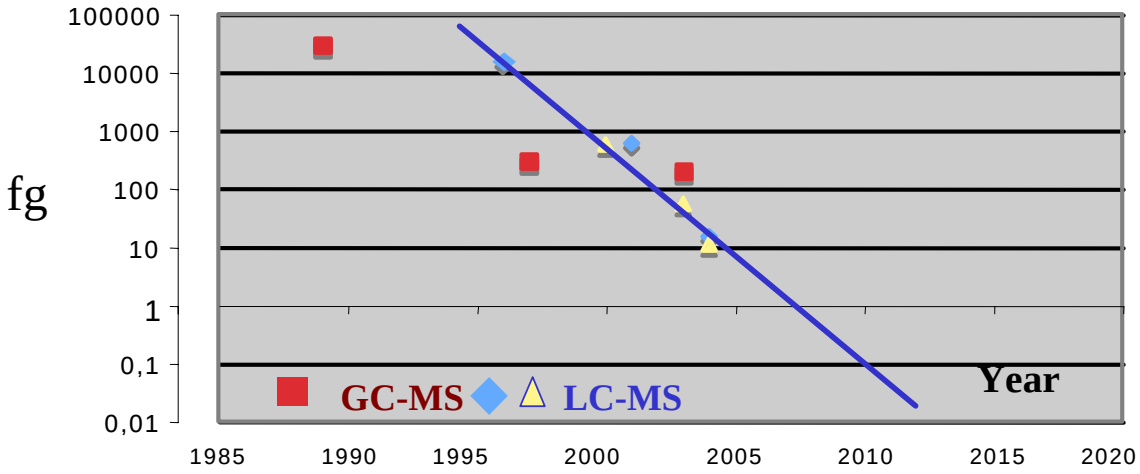

Fig 32.2: Evolution of the limits of detection in function of time

271. The improvement of limits of detection is more pronounced in LC than in GC-MS and will continue with the introduction of new methods of separation and detection. GC and LC-MS should also be used complementary. An illustration with an example: the main metabolite of stanozolol (a synthetic anabolic steroid) in cattle is 16-hydroxystanozolol. This was only observed when samples are also analysed with LC-MS next to GC-MS. Indeed, according to its structure the determination of 16-hydroxystanozolol with GC-MS is very difficult or nearly impossible.

Multi-laboratory study of the analysis and kinetics of stanozolol and metabolites in treated calves. H.F. De Brabander, K. De Wasch, L.A. van Ginkel, S.S. Sterk, M.H. Blokland, Ph. Delahaut, X. Taillieu, M. Dubois, C.J.M. Arts, M.J. van Baak, L. G. Gramberg, R. Schilt , E.O. van Bennekom, D. Courtheyn, J. Vercammen, R.F. Witkamp The Analyst, 123, 12 (1998) 2599-2604.

272. Consequently all data on stanozolol metabolism before the use of LC-MS (1998) have little value because the major metabolite was not detected. There are a number of analogous cases where "older" analytical data should be used with caution. Moreover, when apparatus allowing better separation and/or lower limits of detection become available it is not always possible to repeat expensive animal experiments to update the data.

273. Here is a strong difference between Europa and the US. A difference which can be clearly measured in the citation of literature. Since little researchers in the US work on the determination of residues of banned substances (since they are not banned) publications on these matters (the development of methods) are not cited very much in the US and this could be measured on the citation index.

274. This question refers also to the use of GC-C-IRMS (gas chromatography combustion isotope ratio mass spectrometry). As mentioned in my reply to question 28 the "natural" hormones used for growth promotion purposes are synthetised (prepared) from plant material. In plant material the $^{13}C/^{12}C$ ratio is different from the $^{13}C/^{12}C$ ratio of animals. There are now new data available demonstrating that the pattern change of hormones by the application of the "natural" hormones used for growth promotion purposes.

275. The methods are still in strong evolution –as well in doping control laboratories as in residue analysis. In practice new methods and apparatus need some time to improve technical details in order to improve the robustness of the apparatus. Therefore validation of the methods take considerable time.

33. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), para. 79-80 of EC Rebuttal Submission (Canada case)]

Dr. Boisseau

276. As already mentioned in my reply to the question 29, it is useless to establish MRLs in the absence of ADIs. As, in its 1988 session, JECFA concluded that, given the outcome of its risk assessment for the three natural hormones, there was no need to establish ADIs in order to protect human heath, it was therefore useless to establish MRLs (cf the reply given to the question No 18 which applies also to this question No 33). For the reasons explained in this reply to the question No 18, JECFA decided in 1999 to establish ADIs for these three natural hormones. Usually, establishing ADIs leads to establishing MRLs. In the case of these three natural hormones, the outcome of the assessment of the exposure of consumers by JECFA in 1999 having shown in the reply to question 18 that the highest estimated intake of residue was so low compared with the values of the corresponding ADIs, that there was no need to establish MRLs to protect human health.

277. The residues data considered in 1999 for assessing the exposure were those already used in its thirty second session.

278. If the wording of the conclusions adopted by JECFA has been formally different, the substance of these conclusions remained unchanged.

279. Establishing such ADIs had no specific implications as no MRLs have been established.

280. These new recommendations have not been considered by CCRVDF because CCRVDF did not request JECFA to reassess these hormones and because the new proposals of JECFA did not change the substance of the previous ones.

Dr. Boobis

Reasons for JECFA re-evaluation of the natural hormones

281. The hormones were re-evaluated by the 52nd JECFA on the suggestion of the JECFA Secretariat, due to the availability of new information that had appeared in the published literature since the last evaluation *(FAO, 2000).* This was endorsed by the 11th session of the Codex CCRVDF in their revision of the priority list of substances for review *(CCRVDF, 1998).*

CCRVDF (1998). Report of the Eleventh Session of the Codex Committee on Residues of Veterinary Drugs in Foods, 15-18 September, 1998, Washington, DC: Alinorm 99/31 (http://www.fao.org/docrep/meeting/005/X0203E/x0203e00.htm#Contents)

282. I am unable to comment on whether the residues data were the same as evaluated in 1988.

283. There were a number of additional studies on the toxicology and human (including epidemiological) evaluation of therapeutic exposures to the hormones (e.g. in the form of oral contraception or for hormone replacement therapy) that were not available in 1988.

284. The conclusion of the 1999 JECFA was to establish ADIs for the hormones evaluated whereas in 1988 it was considered unnecessary to allocate ADIs or indeed to prepare toxicological monographs on the hormones. This was presumably because at the time, the view was that it was unnecessary to conduct a detailed evaluation of the toxicology of substances produced endogenously. However, in the intervening time from the first to the second evaluation, it became clear that exposure to the natural hormones, albeit at levels appreciable higher that found in meat from treated cattle, could have adverse effects in humans. Hence, the implicit conclusion was that it was necessary to establish ADIs, to serve as health based guidance values. These could then be used as a benchmark for comparison with exposure via the diet. In JECFA's opinion, exposure at levels up to the ADI daily over a lifetime would be without appreciable risk (IPCS definition of ADI; this is also the CVMP definition of the ADI for a veterinary drug residue (EMEA, 2005)).

285. "Acceptable daily intake (ADI): the estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of bodyweight, that can be ingested daily over a lifetime without any appreciable health risk."

EMEA (2005). Volume 8: Notice to applicants and Guidance: Veterinary medicinal products. Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-8/pdf/vol8_10-2005_.pdf)

286. The data used to establish ADIs for oestradiol and for progesterone in 1999 were from studies in humans that had been undertaken since 1988.

287. According to their report, the CCRVDF did not consider these recommendations because they had not requested the review and found no basis to change their previous decision that MRLs need not be specified for the natural hormones.

> "Recognizing that this Committee had not requested the re-evaluation of these substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, the Committee decided not to consider these new recommendations" *(CCRVDF, 2000)*
>
> *CCRVDF (2000). Report of the Twelfth Session of the CCRVDF (ALINORM 01/31) Washington, D.C., 28-31 March 2000 (http://www.codexalimentarius.net/download/report/217/Al01_31e.pdf)*

288. JECFA establishes ADIs but recommends MRLs. CCRVDF endorsed the recommendation that MRLs for the natural hormones did not need to be specified.

289. The consequence of this decision is that the current status of the Codex MRLs for the three natural hormones is that they are listed as "unnecessary" for tissues from cattle (the species in which the hormones are used).

Dr. De Brabander

290. The driving force after the re-evaluation by the JECFA of the 3 natural hormones can only be guessed (by me). Obviously scientific thinking has evolved in such a way that in 1988 the JECFA found it "unneccessary" to establish ADI's and MRL's for the 3 natural hormones while in 1999 this has changed.

291. The residue data used by the JECFA in 1999 were according to my knowledge the same as those in 1998. Data on residues were generated with radioimmunoassays, which are according to the 2002/657/EC only permitted as screening methods and the validation procedure of the methods can be doubted. The additional information should be from tests on experimental animals and human beings. However, no references to the open literature are given in the 52th JECFA report.

292. The conclusions are different in the fact that ADIs were established: this is recognition of the danger of hormones to human health and welfare in all of his aspects.

293. The last question: Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? It is out of my power to answer.

34. Please comment on the EC argument that the 1999 JECFA report based its findings on (a) outdated residues data and (b) not on evidence from residues in meat but on studies with experimental animals and on general studies of IARC. If the data were not new, did JECFA take this into account in its evaluation? What are the implications of using such data for the purpose of conducting a risk assessment? How reliable are extrapolations from animal studies to possible adverse effects on humans? How does this compare with the kind of data and studies used with respect to other veterinary drugs? [see para. 120 of EC Rebuttal Submission (US case), para. 102 of EC Rebuttal (Canada case)]

Dr. Boisseau

294. As mentioned in my reply to question 33, it is true that (1) the residues data considered by JECFA in 1999 for assessing the exposure were those already used in its thirty second session held in 1987, (2) some of them have not been published in peer-reviewed scientific journals. It is just a banality to say that JECFA is provided with new data when it is requested to assess veterinary drugs recently placed on the market and older data in the case of veterinary drugs already marketed since a

long time ago. Anyway, the quality and the number of the available data are more important than the dates at which these data have been produced. In order to carry out the assessment of the residue exposure and to establish the appropriate MRLs for the substances under review, JECFA has to consider the available data regarding residues. If it considers that the quality and the number of these data, the validation of the analytical methods used to provide these data are satisfactory, JECFA assesses the exposure and establishes MRLs. If it think that it is not the case, it does not establish MRLs and ask for additional data. In the case of hormones, JECFA has considered that the quality and the number of the available residue data were satisfactory and therefore the fact that these data were not new had no specific impact on its evaluation. In addition, the very wide margin of safety between the exposure of consumers to hormones residues and the value of the established ADIs did not raise an acute problem in this case (see my reply to question 18).

295. I don't really understand the meaning of the second EC comment stating that "the toxicological findings in the 1999 JECFA report … are not based on evidence from residues in meat from animals treated with these hormones for growth promotion purposes". As already mentioned in my reply to question 13, toxicological studies are, practically, always carried out with amounts of substances always larger than those corresponding to residues and it is assumed that residues have the same toxicological potential like the tested substances. In the case where there is, among these residues, a metabolite associated with a specific toxicological potential which is of concern with regard to public health, JECFA can base its risk assessment on this metabolite if appropriate and technically possible. Moreover, it is the normal way for assessing the toxicological potential of a substance to take into consideration in vivo studies with experimental animals, in vitro studies and also reports already published by internationally recognized scientific organisations such as IARC.

296. Extrapolation from animals to humans regarding the toxicological potential of the substances under review is not avoidable as it is not possible to carried out experiments in humans. It is the responsability of JECFA to assess to what extent this extrapolation is meaningful for the products under review.

297. For assessing the growth promoters, JECFA has used the same procedure it has used for all the other veterinary drugs.

Dr. De Brabander

298. I think that the EC argument that the JECFA report is based on outdated residue data is correct. I was unable to find in the open scientific literature much modern residue data. Moreover, the laboratories which were able to produce such data and publish them are scarce. Because hormones are banned in Europe and animal experiments on farm animals as cattle are more and more complicated by all kinds of regulations the frequency of these experiments faded out since the 1980's. In the US the intensity of recent data on residue analysis is even more scarce. Only a few US researcher participate in the leading residue conferences which are held in Europe regularly.

299. I haven't seen any impact of studies of the IARC in the JECFA report. However, there are such studies available: a.o. on the website of IARC a recent press release (No 167 of 29 July 2005) could be found: *IARC monographs programme finds combined estrogen-progestogen contraceptives and menopausal therapy are carcinogenic to humans.* This press release illustrates the danger of hormones and also the problematic of synergism: less studies involve combinations of hormones as they are used as production aids (e.g the combination of estradiol and progesterone).

300. Hereunder a citation of the IARC press release

> *"Breast cancer and endometrial cancer are increased. Epidemiological studies consistently demonstrate an increased risk of breast cancer in women who used*

combined menopausal therapy. Largely confined to current or recent users, the risk increases with duration of use and exceeds that in women taking estrogen-only therapy. Endometrial cancer risks depend on the number of days that progestogens are included in the combined therapy. When progestogens are taken fewer than 10 days per month, the risk of endometrial cancer is increased, but when progestogens are taken daily, the risk is similar to that in women who never used hormonal therapy. There was not sufficient evidence to conclude that hormonal therapy has a protective effect at any cancer site.

Overall risks and benefits should be weighed carefully. Both beneficial and adverse effects other than cancer have been established for combined estrogen-progestogen menopausal therapy. As for oral contraceptives, a rigorous risk/benefit analysis would be useful to put the different effects in perspective and assess the overall consequences for public health."

301. The implications of not using such (modern) data are that the results of the risk assessment are biased in favour of the "allowence" of hormones. Giving an answer on the reliability of extrapolations from animal studies to possible adverse effects on humans is and remains difficult. Therefore a safety factor is used.

302. For the comparison with other veterinary drugs (MRLs) the following reasoning could be held. Veterinary (and human) drugs are not used on each animal (as hormones as production aids are) but only in case that they are needed (desease). This is a totally different situation.

35. Please comment on the European Communities claim that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. Is this correct? Have subsequent reports of JECFA, prior or subsequent to the adoption of the Directive, also relied on the same studies? [see para. 171 of EC Rebuttal Submission (US case), para. 161 of EC Rebuttal Submission (Canada case), para. 55, including footnote 60 of US First Submission and Exhibits CDA-20, 33, 34, and 35]

Dr. Boisseau

303. It is correct to say that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. The comment to be made on this issue is similar to the comment already made in the reply to the question 34. JECFA considered a wide series of toxicological studies in its assessment, used as end point a non hormonal effect dose by far more conservative than a NOAEL based on tumorigenic effect and adopted a 200 safety factor to derive an ADI from this NOAEL.

Dr. De Brabander

304. I think that the claim of the European Communities that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s is correct. I scanned the literature on "melengestrol acetate" on the web of science and found only 257 hits. Of these 213 are published in 1980 and later.

305. Of these publications only a few refer to the use of melengestrol acetate as a growth promotor in cattle and therefrom only a few originate from US authors.

Hereunder a selection could be found:

Tepfer AJ, McFee RM, Bott RC, et al.

Feeding melengestrol acetate (MGA) to bulls during the peri or pre-pubertal period induces differences in endocrine profiles which may lead to alterations in testis size.
BIOLOGY OF REPRODUCTION: 225-225 Sp. Iss. SI 2005

Merritt DA, Wilson EM, Martin RA, et al.
Metabolism of melengestrol acetate (MGA) in the bovine: Biological activity assessment of tissue residues and implications for human food safety.
ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY 228: U102-U102 118-AGRO Part 1 AUG 22 2004

Schiffer B, Totsche KU, Jann S, et al.
Mobility of the growth promoters trenbolone and melengestrol acetate in agricultural soil: column studies
SCIENCE OF THE TOTAL ENVIRONMENT 326 (1-3): 225-237 JUN 29 2004

Lange IG, Daxenberger A, Hageleit M, et al.
Non-invasive screening for treatment of heifers with the anabolic steroid melengestrol acetate (MGA) by feces analysis
JOURNAL OF IMMUNOASSAY & IMMUNOCHEMISTRY 24 (3): 265-272 AUG 2003

Schiffer B, Daxenberger A, Meyer K, et al.
The fate of trenbolone acetate and melengestrol acetate after application as growth promoters in cattle: Environmental studies
ENVIRONMENTAL HEALTH PERSPECTIVES 109 (11): 1145-1151 NOV 2001

Hageleit M, Daxenberger A, Meyer HHD
A sensitive enzyme immunoassay (EIA) for the determination of melengestrol acetate (MGA) in adipose and muscle tissues
FOOD ADDITIVES AND CONTAMINANTS 18 (4): 285-291 APR 2001

Daxenberger A, Meyer K, Hageleit M, et al.
Detection of melengestrol acetate residues in plasma and edible tissues of heifers
VETERINARY QUARTERLY 21 (4): 154-158 OCT 1999

Karg H, Meyer HHD
Update evaluation of trenbolone acetate, zeranol and melengestrol acetate as growth promoters (considerations concerning the "hormone issues" between EU and USA at the WTO)
ARCHIV FUR LEBENSMITTELHYGIENE 50 (2): 28-37 MAR-APR 1999

Henricks DM, Brandt RT, Titgemeyer EC, et al.
Serum concentrations of trenbolone-17 beta and estradiol-17 beta and performance of heifers treated with trenbolone acetate, melengestrol acetate, or estradiol-17 beta
JOURNAL OF ANIMAL SCIENCE 75 (10): 2627-2633 OCT 1997

CAMPBELL HM, SAUVE F
LIQUID-CHROMATOGRAPHIC DETERMINATION OF MELENGESTROL ACETATE IN FEEDS
JOURNAL OF AOAC INTERNATIONAL 76 (6): 1163-1167 NOV-DEC 1993

NEIDERT EE, GEDIR RG, MILWARD LJ, et al.
DETERMINATION AND QUALITATIVE CONFIRMATION OF MELENGESTROL ACETATE RESIDUES IN BEEF FAT BY ELECTRON-CAPTURE GAS-

CHROMATOGRAPHY AND GAS-CHROMATOGRAPHIC CHEMICAL IONIZATION MASS-SPECTROMETRY
JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY 38 (4): 979-981 APR 1990

CHICHILA TMP, EDLUND PO, HENION JD, et al.
DETERMINATION OF MELENGESTROL ACETATE IN BOVINE-TISSUES BY AUTOMATED COUPLED-COLUMN NORMAL-PHASE HIGH-PERFORMANCE LIQUID-CHROMATOGRAPHY
JOURNAL OF CHROMATOGRAPHY-BIOMEDICAL APPLICATIONS 488 (2): 389-406 MAR 24 1989

KRZEMINSKI LF, COX BL, GOSLINE RE
FATE OF RADIOACTIVE MELENGESTROL ACETATE IN THE BOVINE
JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY 29 (2): 387-391 1981

306. Also: If you look at the "International Portal on Food Safety, Animal & Plant Health" http://www.ipfsaph.org/servlet/CDSServlet?status=ND1jdGh0dHB3d3dmYW9vcmdhb3NpcGZzYXBoaW5mb3JtYXRpb25zb3VyY2VqZWNmYS5KRUNGQUVWQUxtZWxlbmdlc3Ryb2xhY2V0YXRlJjY9ZW4mMzM9Zm9ybWFsX3RleHQmMzc9aW5mbw~~ the three pdf files relating melengestrol acetate, which can be downloaded contain only "old" references (before 1980).

(c) Dose-response relationship

36. How would you describe a dose-response assessment? Is it, as suggested by Canada in para. 78 of its Rebuttal Submission, "widely, if not universally, accepted that adverse effects arising from hormonal activities are dose-dependent"? Is dose-response assessment a necessary component of hazard characterization? Or, is there an alternative approach which can replace the dose-response assessment. Is a dose-response assessment feasible/necessary for substances that are found to be genotoxic or to have genotoxic potential? [see para. 153 of EC Replies to Panel Questions, para. 200 of EC Rebuttal Submission (US case); paras. 143, 154, and 156 of US First Submission, paras. 70-74 of US Replies to Panel Questions, and paras. 34 and 37-40 of US Rebuttal Submission; paras. 76-82 of Canada Rebuttal Submission]

Dr. Boisseau

307. The comment made by Canada regarding the dose response relationship is correct. Dose-response assessment is a necessary component of hazard characterisation and there is, to my knowledge, no alternative approach which can replace this dose- response assessment. A dose-response assessment is not feasible for substances that are found to be genotoxic or to have genotoxic potential if, as it has been already said in the reply to the question No 19, these substances are xenobiotics and if it is thought that this genotoxic potential can be expressed in in vivo conditions.

Dr. Boobis

308. Dose-response assessment is analysis of the relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub)population and the changes developed in that organism, system or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population *(IPCS, 2004)*. In a dose-response assessment, information that is sought includes whether there is evidence for a compound-dependent effect, if so, the dose range over which these effects occur, the quantitative relationship between dose and the magnitude or incidence of the effect, the steepness of the dose-response curve, the severity or incidence of the maximum effect observed, whether there is a threshold and if so its location and the

spacing between the no observable adverse effect level (NOAEL) and the lowest observable adverse effect level LOAEL).

309. It is generally accepted that adverse effects arising from hormonal activities are dose-dependent *(IUPAC, 2003)*. The caveat is that this is when the response is mediated by the physiological mechanisms of the hormone, via receptor occupancy. However, even should this not be the case because of a genotoxic mode of action, the response would depend on dose. The difference would be in the shape of the dose response curve. In the former, there would be a threshold, a dose below which there would be no effect (NOAEL). In the latter, there would not necessarily be a such a threshold. Hence, although risk would diminish as dose decreases, it may never reach zero.

IUPAC(2003). Special Topic Issue on the Implications of Endocrine Active Substances for Humans and Wildlife, Pure Appl. Chem., Vol. 75, Nos. 11–12

310. In risk assessment, dose-response assessment is an essential part of hazard characterization, as it forms the basis for deriving health-based guidance values such as the ADI, with which dietary intake can be compared. The only exception would be a hazard-based approach, that is recommendations as to potential safety based on intrinsic capacity to cause harm rather than on the probability of harm occurring. The former can be based on hazard identification whilst the latter requires hazard characterization and exposure assessment. The most widely used instance of hazard-based safety guidance is that for substances that are genotoxic or that have genotoxic potential. However, this needs to be qualified, in that not all such substances would be treated in this way. This is discussed in my reply to question 19 above. There may be kinetic (e.g. phenol following oral exposure, *European Chemicals Bureau, 2006*) or dynamic (e.g. spindle inhibitors such as thiophanate-methyl, *EC, 2005a)* reasons why a genotoxic compound exhibits a threshold in its dose-response relationship. Similarly, compounds that are genotoxic via the formation of reactive oxygen species also exhibit a threshold in their dose-response curve *(Brusick, 2005)*. Such effects would be treated as would non-genotoxic endpoints, i.e. an ADI would be established using the threshold dose (NOAEL) as a starting point, and appropriate uncertainty factors. Where the mechanism of genotoxicity is not known, DNA reactivity is assumed. However, for compounds that are known or assumed to be genotoxic via DNA reactivity, genotoxic potential would normally have to be confirmed in vivo before this endpoint would be used as the basis for a risk assessment *(CVMP, 2004)*. For such compounds, unless there is good evidence to the contrary, it is assumed that there is no threshold for the dose-response curve.

311. The approach for such compounds that are known or assumed to exhibit no threshold in their dose-response curve, varies from one region to another. In Europe and generally within JECFA, once a compound is identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action, no exposure is considered without risk, and hence a recommendation of maintaining intake as low as reasonable practicable (ALARP) may be made, without any consideration of the dose-response relationship. In the case of a veterinary drug residue the simplest way to achieve ALARP would be not to use the drug in veterinary practice. In other regions, such as the USA, appropriate dose-response assessment will be undertaken, using an approach that assumes no threshold (linear, low dose extrapolation). In this approach, if intake is below that associated with a very low risk (often an incidence of 1 in 10^6 of the population), exposure may be considered acceptable *(US EPA, 2005; US FDA, 2005).*

US FDA, Guideline No. 3, 2005. General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals (http://www.fda.gov/cvm/Guidance/GFI003.htm)

US EPA, 2005. Guidelines for Carcinogen Risk Assessment (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=439797)

Dr. Cogliano

312. Dose-response assessment is a quantitative characterization of the relationship between the dose of an agent and the occurrence of adverse effects. In my view, it is widely accepted that adverse effects arising from hormonal activities depend on the dose; that is, the level of effect depends on the level of exposure. Dose-response assessment is not, however, a necessary component of hazard characterization. Without a dose-response assessment, it is possible to conclude that an agent can alter the risk of one or more adverse effects. With a dose-response assessment, it may also be possible to estimate how much the risk may be altered for a given level of exposure.

37. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "...while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents..."? [see Exhibit CDA-25]

Dr. Boisseau

313. JECFA has always established ADIs for veterinary drugs on the basis of a dose-response assessment. As already said in the reply to the question No 7, JECFA did not establish any ADI when it was not possible to carry out a dose-response assessment such as with xenobiotic compounds such as chloramphenicol and nitroimidazoles.

Dr. Boobis

Is dose-response assessment optional?

314. Codex and JECFA materials certainly require that a dose-response assessment should always be conducted as part of the risk assessment of a chemical agent *(CAC, 2005; IPCS: EHC 70, 1987 and EHC 104, 1990; IPCS, 2005; WHO, 1996 and 2001)*. JECFA would be unable to recommend MRLs (or conclude that they need not be specified) unless it had quantitative information on the levels of exposure that were considered not to cause harm (from either observations in humans and/or studies in experimental animals) and an estimate of actual human exposure. If JECFA concluded that the toxicity of a compound was without threshold because it was a genotoxic carcinogen of potential relevance to humans (the default assumption), it may well conclude that it would be inappropriate to recommend MRLs, and hence in this specific circumstance a dose-response assessment might be considered unnecessary. However, this is a very unlikely occurrence for a veterinary drug because, in general, producers tend to screen out genotoxic compounds during the development process. This is not to say that such drugs will never be encountered, but simply to point out that there are procedures in place that are such that they will substantially reduce the probability of this occurring.

(d) Sensitive populations

38. Please describe the range of physiological (or background) levels of the sex hormones in humans and identify the variations in these levels on the basis of age, sex group, and physiological stages.

Dr. Boisseau

315. According to several scientific publications reported by the SCVPH in its 1999 Opinion, the endogenous steroid hormone levels in human females and males are the following:

Hormone	Women Prepubertal	Women Follicular-Luteal	Women Postmenopausal	Men Prepubertal	Men Adult
Oestradiol pg/ml	8-23	10-375	0-28	5-14	6-44
Estrone pg/ml	19	15-250	15-55	16	15-65
Progesterone ng/ml	0.1-0.4	0.2624		0.1-0.3	0.3-0.5
Testosterone ng/ml	0.1-0.2	0.4-0.8	0.4-0.8	0.1-0.2	3-9

316. According to the data reported by JECFA, in its 32nd session held in 1987, and by the SCVPH in its 1999 Opinion, the daily production rates for hormones in human females and males are the following:

Hormone	Women Prepubertal	Women Follicular	Women Pregnancy	Men Prepubertal	Men Adult
Oestradiol µg/day		445	37.800	6,5	48
Progesterone µg/day		418	94.000	150	416
Testosterone µg/day	32-65	140-240		32-65	6.500

317. According to the SCVPH in its 1999 Opinion, new ultrasensitive bioassays, 100 fold more sensitive than RIA methods used to provide the data reported in the above tables, would lead to lower values, respectively 0.6 pg/ml and 0.08 pg/ml of oestradiol-17β for prepubertal girls and boys. It would be important to know whether these new bioassays have been properly validated as this SCVPH Opinion says nothing about that and wether the data obtained with these methods for both men and women are also totally different from those obtained with the RIA methods.

39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol-17β and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the populations which have been identified as particularly sensitive such as prepubertal children" [see para. 147 of the EC Replies to Panel Questions]

Dr. Boisseau

318. As already said in my reply to question 31, the comment of SCVPH needs to integrate a quantitative assessment of the risk associated with this excess exposure for the groups of populations which have been identified as particularly sensitive such as prepubertal children. This excess exposure of these sensitive populations needs to be assessed and compared with the exposure resulting from the daily consumption of meat from cattle which have not been treated by growth promoters, from other food and products of animal origin and from their own production of hormones.

Dr. Sippell[2]

319. The SCVPH opinion that "any excess exposure towards estradiol-17ß … prepubertal children" is supported by increasing evidence from more recent scientific data in the international literature, both from Europe and from America. Due to the almost 100 times lower estradiol-17ß (E_2) serum levels found by modern ultrasensitive assay techniques (Klein et al 1994, Larmore et al 2002) in prepubertal children as compared to conventional E_2 assays, the resulting potential E_2 exposure risk from consumption of meat and meat products has greatly increased by a factor of at least 160 times, if one compares the maximum acceptable daily intake (ADI) estimates of E_2 of 65 ng/day (old) and 0.4 ng/day (new) in prepubertal boys (Andersson & Skakkebaek, 1999). This revised ADI threshold would be reached already after ingestion of as little as 10 g of E_2 –treated meat from cattle

[2] A full list of references cited in responses from Dr. Sippell can be found in Attachment 2.

(Daxenberger et al 2001). Moreover, in this comparison only E_2 but not its numerous estrogenic metabolites, glucosidic conjugates and fatty acid esters (Maume et al 2001) were taken into account.

320. It has been shown in numerous scientific publications in vitro, in vivo and in the human that infants and prepubertal children are highly sensitive to increased E_2-levels, resulting in premature breast development (Schmidt et al 2002), growth acceleration (Lampit et al 2002), earlier sexual maturation in girls, in particular in the USA (Sun et al 2002, WU et al, 2002) and less in Europe (Muinck-keizer & Mul 2001), and the well known significantly higher incidence of precocious puberty in girls than in boys (Teilmann et al 2005). Accidental exposure of prepubertal boys to estrogens has resulted in gynecomastia and advanced bone maturation (Felner & White 2000).

321. Late effects: There is now increasing epidemiological evidence that exposure to elevated estrogen levels during early life (pre- and postnatally) carries an increased risk of breast cancer in adult life (Ekbom et al 1997, Swerdlow et al 1997, Weiss et al 1997, Halakivi-Clarke et al 2000), whereas conditions with low E_2 levels, such as preeclampsia, seem to have a protective effect (Innes & Byers 1999). Moreover, indirect evidence suggests that male reproductive disorders such as testicular cancer, cryptorchidism, hypospadias and poor sperm quality may also have their origin in hormonal disturbances induced by E_2 and/or estrogenic substances during fetal life (Skakkebaek et al 2001) and also during childhood (Higuchi et al 2003, Ramaswamy 2005).

Andersson AM & Skakkebaek NE (1999) Exposure to exogenous estrogens in food: possible impact on human development and health. Eur. J. Endocrinol. 140, 477-485.

Daxenberger A, Ibarreta D & Meyer HH (2001) Possible health impact of animal oestrogens in food. Hum. Reprod. Update. 7, 340-355.

Ekbom A, Hsieh CC, Lipworth L, Adami HQ & Trichopoulos D (1997) Intrauterine environment and breast cancer risk in women: a population-based study. J. Natl. Cancer Inst. 89, 71-76.

Felner EI & White PC (2000) Prepubertal gynecomastia: indirect exposure to estrogen cream. Pediatrics 105, E55.

Halakivi-Clarke L, Cho E, Onojafe I, Liao DJ & Clarke R (2000) Maternal exposure to tamoxifen during pregnancy increases carcinogen-induced mammary tumorigenesis among female rat offspring. Clin. Cancer Res. 6, 305-308.

Higuchi TT, Palmer JS, Gray LE, Jr. & Veeramachaneni DN (2003) Effects of dibutyl phthalate in male rabbits following in utero, adolescent, or postpubertal exposure. Toxicol. Sci. 72, 301-313.

Innes KE & Byers TE (1999) Preeclampsia and breast cancer risk. Epidemiology 10, 722-732.

Klein KO, Baron J, Colli MJ, McDonnell DP & Cutler GB, Jr. (1994) Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. J. Clin. Invest 94, 2475-2480.

Lampit M, Golander A, Guttmann H & Hochberg Z (2002) Estrogen mini-dose replacement during GnRH agonist therapy in central precocious puberty: a pilot study. J. Clin. Endocrinol. Metab 87, 687-690.

Larmore KA, O'Connor D, Sherman TI, Funanage VL, Hassink SG & Klein KO (2002) Leptin and estradiol as related to change in pubertal status and body weight. Med. Sci. Monit. 8, CR206-CR210.

Maume D, Deceuninck Y, Pouponneau K, Paris A, Le Bizec B & Andre F (2001) Assessment of estradiol and its metabolites in meat. APMIS 109, 32-38.

Muinck-Keizer SM & Mul D (2001) Trends in pubertal development in Europe. Hum. Reprod. Update. 7, 287-291.

Ramaswamy S (2005) Pubertal augmentation in juvenile rhesus monkey testosterone production induced by invariant gonadotropin stimulation is inhibited by estrogen. J. Clin. Endocrinol. Metab 90, 5866-5875.

Schmidt IM, Chellakooty M, Haavisto AM, Boisen KA, Damgaard IN, Steendahl U, Toppari J, Skakkebaek NE & Main KM (2002) Gender difference in breast tissue size in infancy: correlation with serum estradiol. Pediatr. Res. 52, 682-686.

Skakkebaek NE, Rajpert-De Meyts E & Main KM (2001) Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum. Reprod. 16, 972-978.

Teilmann G, Pedersen CB, Jensen TK, Skakkebaek NE & Juul A (2005) Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. Pediatrics 116, 1323-1328.

40. The European Communities states that "the levels of endogenous production of the hormones by prepubertal children is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship..." Please comment on the methodology used by the SCVPH to support the conclusion that hormone levels are lower than previously thought, and in particular comment on the validity of these methodologies and their conclusions. Would your conclusions have been the same at the time of adoption of the Directive in September 2003?

Dr. Boisseau

322. My comment given at the end of question 38 replies to this question.

323. My reply would not have been different at the time of adoption of the EC Directive in September 2003.

Dr. Boobis

Hormone production in prepubertal children

324. There is certainly some evidence that endogenous levels of hormones in children are lower than previously thought. However, the suggestion that this is by orders of magnitude is not substantiated by the data. One group has reported very low levels of oestradiol in male children, 0.08 pg/ml *(Klein et al, 1994)*, but in a later study *(Klein et al, 1998)*, the same group reported mean levels somewhat higher, at 0.27 pg/ml. The reliability of the Klein et al assay has yet to be determined. The assay is particularly sensitive to oestradiol, but there is no obvious explanation for this, as it relies upon affinity for the oestrogen receptor. Diethylstilbestrol is a potent oestrogen yet is

much less sensitive than oestradiol in the assay. *Klein et al (1994)* have reported that there are unidentified factors in plasma and in blood collection tubes that can interfere in the assay. In contrast, using a similar yeast-based assay, *Coldham et al (1997)* found that oestradiol and DES had similar potency, and other have found that, if anything, DES is more potent that oestradiol in such assays *(Folmer et al, 2002).* At the very least, this shows that results with the yeast reporter assay are not consistent, and use of such data in risk assessment requires that the assay be adequately validated.

Coldham NG, Dave M, Sivapathasundaram S, McDonnell DP, Connor C and Sauer MJ (1997). Evaluation of a recombinant yeast cell estrogen screening assay. Environ Health Perspect, 105:734-742

Folmar LC, Hemmer MJ, Denslow ND, Kroll K, Chen J, Cheek A, Richman H, Meredith H and Grau EG (2002). A comparison of the estrogenic potencies of estradiol, ethynylestradiol, diethylstilbestrol, nonylphenol and methoxychlor in vivo and in vitro. Aquat Toxicol, 60:101-110

Klein KO, Baron J, Colli MJ, McDonnell DP and Cutler GB Jr (1994). Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. J Clin Invest, 94:2475-2480

Klein KO, Baron J, Barnes KM, Pescovitz OH and Cutler GB Jr (1998). Use of an ultrasensitive recombinant cell bioassay to determine estrogen levels in girls with precocious puberty treated with a luteinizing hormone-releasing hormone agonist. J Clin Endocrinol Metab, 83:2387-2389

325. However, there are studies from two other groups using more specific methods than the original radioimmunoassay, reporting that levels were somewhat higher than this. *Ikegami et al (2001)* used a very sensitive, 2-stage immunoassay technique. This was shown to be specific and sensitive. In this assay, mean levels of oestradiol in prepubertal males were 1.85 pg/ml (6.8 pmol/ml). *Paris et al (2002)* used a recombinant oestrogen receptor assay in a mammalian cell line, a similar principle to the assay of Klein et al. In this study, estogenic levels in prepubertal males were found to be 1.44 pg/ml. There are many issues affecting such measurements. These include the presence of binding proteins, relative specificity and sensitivity. None of the assays is entirely specific for oestradiol. Both the oestrogen receptor and the antibodies used could cross-react with structurally related compounds. Depending on how the assay is performed, protein binding could reduce the concentration of hormone detectable in the assay by sequestering hormone from the assay target. However, it should be noted that whilst binding to protein in plasma my reduce clearance it will also reduce the biologically active dose. In general, it is the free concentration that determines biological activity *(Teeguarden and Barton, 2004).* Hence, if SHBG is elevated in children this would tend to reduce the effect of an equivalent total plasma concentration by reducing the free concentration.

326. The advantage of the recombinant assays is that they measure biologically active material, whereas the immunoassays may include cross-reacting less or inactive metabolites. Whilst the recombinant assays may include hormonally active material other than the specific analyte, this does provide an indication of to what the body is exposed in vivo. Hence, on balance, the data of *Paris et al (2002)* may be the most meaningful to date. This presumably reflects circulating total active oestrogenic material, but not that bound to proteins.

Ikegami S, Moriwake T, Tanaka H, Inoue M, Kubo T, Suzuki S, Kanzakili S and Seino Y (2001). An ultrasensitive assay revealed age-related changes in serum oestradiol at low concentrations in both sexes from infancy to puberty. Clin Endocrinol (Oxf), 55:789-795

Paris F, Servant N, Terouanne B, Balaguer P, Nicolas JC and Sultan C (2002). A new recombinant cell bioassay for ultrasensitive determination of serum estrogenic bioactivity in children. J Clin Endocrinol Metab, 87:791-797

Teeguarden JG and Barton HA (2004). Computational modeling of serum-binding proteins and clearance in extrapolations across life stages and species for endocrine active compounds. Risk Anal, 24:751-770

327. Assuming a plasma concentration of 1.44 pg/ml *(Paris et al, 2002),* this would be equivalent to a daily oestradiol production of 2 µg/day. These data suggest that exposure to oestradiol at levels near the JECFA ADI of 50 ng/kg, equivalent to 1.3 µg/day (assuming a body weight of 26 kg) could result in intakes close to the daily production of oestradiol in prepubertal males, the group suggested to be most at risk. However, this exposure is via the oral route, and bioavailability by this route is very low (<5%) *(Fortherby, 1996).* In addition, very little of the absorbed hormone will be free, over 95% being bound to plasma proteins such as SHBG. Such binding reduces the biological activity of the hormone *(Teeguarden and Barton, 2004).* Hence, the JECFA ADI would appear to be appropriate for all groups of the population. This conclusion would have been the same at the time of adoption of the Directive by the EC in September 2003.

Dr. Sippell

328. There is no doubt that the development of an ultrasensitive recombinant cell bioassay (RCBA) of E_2 by Karen Klein, Gordon Cutler and co-workers at the N.I.H. in Bethesda, USA (Klein et al 1994) represented a quantum leap in E_2 assay methodology. It opened a new door on our understanding of basic physiological phenomena, e.g. why normal puberty starts so much earlier in girls than in boys or why bone maturation in children differs so much between the sexes. The validity of the N.I.H.-RCBA has now been confirmed by another RCBA of E_2 which was developed by Charles Sultan's group at the University of Montpellier, France (Paris et al 2002). Unfortunately, the complexity of the RCBA so far prevents its wider use for routine measurements in small serum samples from infants and prepubertal children.

329. Since pediatric endocrinologists and other researchers in the field had already been hearing and discussing these breakthrough findings since 1993/94, and again in 2001/02, I would certainly have come to the same conclusions in September 2003.

Klein KO, Baron J, Colli MJ, McDonnell DP & Cutler GB, Jr. (1994) Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. J. Clin. Invest 94, 2475-2480.

Paris F, Servant N, Terouanne B, Balaguer P, Nicolas JC & Sultan C (2002) A new recombinant cell bioassay for ultrasensitive determination of serum estrogenic bioactivity in children. J. Clin. Endocrinol. Metab 87, 791-797.

41. Why would individuals with the lowest endogenous hormone levels be at greatest risk? How would the risks for these individuals arising from hormones naturally present in meat differ from the risks arising from the residues of hormone growth promoters?

Dr. Boisseau

330. Individuals with the lowest endogenous hormone levels have been considered as being at greater risk by JECFA because the rationale followed by JECFA was, in the case of natural hormones, to avoid that any excess intake of hormonally active residues be significant with regard to the rate of their daily production of hormones in order to protect them from any physiological disturbance. In this respect, the target was that the hormonal residue intake does not account for more than 1% of the daily production rate of any group of the human population. Therefore, the lower is the endogenous production of hormones in a given human group, the lower must be the excess intake of hormonally active residues for the individuals of this group.

331. From a qualitative point of view, the risks for these individuals arising from residues resulting from the use of hormones growth promoters in cattle does not differ from the risks arising from the residues of hormones naturally present in meat. The potential problem which may exist is only a quantitative one.

Dr. Boobis

Relevance of endogenous hormone levels to risk

332. The reason that those with the lowest levels of hormone production are considered at the greatest risk is because for a given exposure this group will experience the greatest percentage change in their circulating hormone levels. There is evidence that the levels are normally low in such subjects to ensure a biological effect that is no greater than that appropriate to their gender and age. Hence, the extent of the biological response is likely to reflect the percentage increase in hormone levels. In addition, prior to puberty, some biological systems are more sensitive to hormonal perturbation than after puberty *(Caruso-Nicoletti et al, 1985; Miyamoto and Burger, 2003).*

Caruso-Nicoletti M, Cassorla F, Skerda M, Ross JL, Loriaux DL and Cutler GB Jr (1985). Short term, low dose estradiol accelerates ulnar growth in boys. J Clin Endocrinol Metab, 61:896-898

333. There is no basis to think that the effect of hormone growth promoters would be different in any way whatsoever from hormones naturally present in meat, at equivalent internal exposure levels.

Dr. Sippell

334. This question relating to the specific vulnerability of young children having the lowest levels of endogenous hormones (estradiol, testosterone, progesterone and their metabolites) has largely been answered above (see my reply to question no. 39).

335. The risk to children arising from hormones which are naturally present in meat as compared to that from residues of hormonal growth promoters has, to my knowledge, been estimated for E_2 only and only in beef (Daxenberger et al 2001). The average E_2 content of 500 g of meat (standard daily consumption of 300 g muscle, 100 g liver, 50 g kidney and 50 g fat according to JECFA) was 4.3 ng and 20 ng of E_2 in untreated and E_2-treated cattle, respectively. The new threshold of 0.4 ng E_2 /day would thus be reached after the ingestion of 47 g of untreated meat and of as little as 10 g of hormone treated meat. These authors also estimated that eating meat from E_2 –treated cattle increased the daily intake of E_2 from food by 38% compared to non-treated meat. This percentage, and thus the potential health risk, will be considerably higher if the food intake from pork, poultry, eggs and dairy products derived from E_2 –treated farm animals are taken into account.

336. Synthetic hormone growth promoters such as Zeranol and its metabolites have been shown to be as potent as E_2 and diethylstilbestrol (DES) in increasing the expression of estrogen-related genes in human breast cancer cells (Leffers et al 2001). On the other hand, the synthetic androgen Trenbolone and the gestagen Melengestrol bind with high affinity to the human androgen and progesterone receptors, respectively (Bauer et al 2000). Exposure during pregnancy might result in severe transplacental virilisation of a female fetus.

Bauer ER, Daxenberger A, Petri T, Sauerwein H & Meyer HH (2000) Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and to the bovine progestin receptor. APMIS 108, 838-846.

Daxenberger A, Ibarreta D & Meyer HH (2001) Possible health impact of animal oestrogens in food. Hum. Reprod. Update. 7, 340-355.

Leffers H, Naesby M, Vendelbo B, Skakkebaek NE & Jorgensen M (2001) Oestrogenic potencies of Zeranol, oestradiol, diethylstilboestrol, Bisphenol-A and genistein: implications for exposure assessment of potential endocrine disrupters. Hum. Reprod. 16, 1037-1045.

42. To what extent, in your view, has JECFA taken into account the particular situation of sensitive populations, in particular prepubertal children, in its risk assessments with respect to oestradiol-17β? Please compare the original data concerning endogenous production of natural hormones by prepubertal children upon which JECFA based its assessment and those used by the European Communities in its risk assessment. In your view, does the scientific material referred to by the European Communities require a revision of the Codex recommendation with respect to oestradiol-17β?

Dr. Boisseau

337. Individuals with the lowest endogenous hormone levels have been considered as being at greater risk by JECFA because the rationale followed by JECFA was, in the case of natural hormones, to avoid that any excess intake of hormonally active residues be significant with regard to the rate of their daily production of hormones in order to protect them from any physiological disturbance. In this respect, the target was that the hormonal residue intake does not account for more than 1% of the daily production rate of any group of the human population. Therefore, the lower is the endogenous production of hormones in a given human group, the lower must be the excess intake of hormonally active residues for the individuals of this group.

338. From a qualitative point of view, the risks for these individuals arising from residues resulting from the use of hormones growth promoters in cattle does not differ from the risks arising from the residues of hormones naturally present in meat. The potential problem which may exist is only a quantitative one.

Dr. Boobis

Consideration of sensitive populations by JECFA

339. In keeping with its risk assessment principles, the ADI established by JECFA would have been designed to protect all segments of the population, including prepubertal children (*IPCS: EHC 70, 1987 and EHC 104, 1990; IPCS, 2005; WHO, 1996 and 2001).* For this reason, in establishing the ADI from the NOAEL in a human study, JECFA used a 10-fold safety factor to protect sensitive populations, in addition to a 10-fold factor to allow for interindividual variation within the adult human population. For an evaluation of the impact of differences in assumed endogenous production of hormones by JECFA and the EC on the risk assessment see my reply to question 40 above.

340. In my view, there is no requirement for any revision in the Codex recommendation with respect to oestradiol-17β on the basis of the material referred to by the EC.

Dr. Sippell

341. To my knowledge, the particular situation of sensitive populations, in particular infants and prepubertal children, has not been adequately taken into account by JECFA in respect of E_2.

342. The original data on prepubertal children used by JECFA have been questioned in a number of more recent publications (Andersson & Skakkebaek 1999, Maume et al 2001, Partsch & Sippell

2001) in view of the new ADI based on the ultrasensitive RCBA determination of E_2 in children. The data have already been compared in the answer to questions 39 and 41.

343. In my view, the scientific material referred to by the European Communities definitely requires a revision of the codex recommendation with respect to E_2, as outlined above.

Andersson AM & Skakkebaek NE (1999) Exposure to exogenous estrogens in food: possible impact on human development and health. Eur. J. Endocrinol. 140, 477-485.

Maume D, Deceuninck Y, Pouponneau K, Paris A, Le Bizec B & Andre F (2001) Assessment of estradiol and its metabolites in meat. APMIS 109, 32-38.

Partsch CJ & Dr. Sippell WG (2001) Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. Hum. Reprod. Update. 7, 292-302.

[For the questions in this section, see paras. 121-122 of EC Rebuttal Submission (US case), paras. 103-104 of EC Rebuttal Submission (Canada case), Exhibits EC-88, 99, paras. 42-45 of US Rebuttal Submission, paras. 84 and 159 of US First Submission, and for JECFA's work Exhibits CDA 11, 16, 17, 18, 39]

(e) Bioavailability

43. Please define bioavailability, comment on the significance of bioavailability to assessments of risk, and on the degree of bioavailabilitiy of the residues of the hormones at issue when consumed in meat, taking into account parties' differing views on this matter. [see paras. 123-124 of EC Rebuttal Submission (US case), para. 105-106 of EC Rebuttal Submission (Canada case), paras. 100, 155-159 of the EC Replies to Panel Questions, paras. 32 and 41-42 of US Rebuttal Submission, paras. 69, 71, 88-89 and 146 of US First Submission, and para. 134 of Canada Rebuttal Submission]

Dr. Boisseau

344. Bioavailability is the capacity of a substance to enter the general blood circulation and to diffuse into the whole body of the animal or the human being administered this substance. The physico-chemical characteristics of substances and their route of administration to humans and animals are of a paramount importance regarding the rate at which they are bioavailable. Oral route, which is the route for the ingestion of residues, is not the most efficient. It is even very poor for the three natural hormones.

345. The bioavailability of residues has to be taken into consideration in the risk asessment, in particular at the third step regarding the exposure assessment of residues. Residues which are not bioavailable are not of concern for the public health if the toxicological potential of the substance is a systemic one. The residues, the bioavailability of which has not been determined, are considered as totally bioavailable. Those which have been recognised as non bioavailable can be discarded from the exposure assessment.

346. Natural hormones are known to be poorly bioavailable in humans : oestradiol-17β is inactive orally, the bioavailability of progesterone and of testosterone are respectively less than 10% and around 4%.

347. The bioavailability of melengestrol, trenbolone and zeranol residues have not been determined.Therefore all their residues have been considered as being totally bioavailable.

Dr. Boobis

348. Bioavailability can be defined as that fraction of a dose that is available to the systemic circulation. It can take values from 0, no systemic availability, to 1, 100% availability. It is normally estimated by comparing the dose-corrected area under the plasma concentration time curve (AUC) after dosing by the route of interest, for example orally, with the dose-corrected AUC after intravenous administration (assumed to be completely available) *(Rowland and Tozer, 1995).* The bioavailability reflects both the extent of absorption and any presystemic metabolism that occurs. In the case of the oral route, this could be in the intestinal tract and/or the liver

Rowland M and Tozer T (1995). Clinical Pharmacokinetics: Concepts and Applications, Lippincott Williams and Wilkins, London

349. In general, only that fraction of the dose that is bioavailable is toxicologically relevant. The exceptions would be when some or all of the non-bioavailable dose is in the form of a bioavailable metabolite that is biologically active, or when the effects of concern occur presystemically, for example local effects on the gastrointestinal mucosa. In the case of the natural hormones, low bioavailability is due to presystemic metabolism to products with substantially reduced hormonal activity and their bioavailability is <5-10% (*Christiaens et al, 2005; Hoogenboom et al, 2001; JECFA, 2000; Jockenhövel, 2002;Kuhnz et al, 1993; Stanczyk, 2003).* The effects of concern are systemic. Hence, the toxicological significance of the low bioavailability of hormones is that the risk is less than from the equivalent dose produced endogenously or administered by some other route with higher bioavailability (e.g. subcutaneous implant).

*Christiaens V, Berckmans P, Haelens A, Witters H and Claessens F (2005). Comparison of different androgen bioassays in the screening for environmental (anti)androgenic activity. Environ Toxicol Chem, **24**:2646-2656*

*Hoogenboom LAP, de Haan L, Hooijerink D, Bor G, Murk AJ and Brouwer A (2001). Estrogenic activity of estradiol and its metabolites in the ER-CALUX assay with human T47D breast cells. APMIS, **109**:101-107*

*Jockenhövel F (2002). Practical aspects of testosterone substitution. Aging Male, **5** (Suppl 1):21–46*

*Stanczyk FZ (2003). All progestins are not created equal. Steroids, **68**:879-890*

350. However, low bioavailability does not necessarily increase the margin of safety (the ratio of ADI to actual exposure). This is because the effects of concern are usually determined following exposure by the route of interest, in this case oral. Hence, the ADI represents a "bioavailability adjusted" dose, just as the TMDI does. The consequence of this is that anything that increases bioavailability will reduce the margin of safety whilst anything that reduces bioavailability will increase the margin of safety. In the case of the natural hormones, changes in bioavailability are likely to be a consequence of changes in the enzymes of metabolism in the liver and/or small intestine.

351. The bioavailability of the non-natural hormones (melengestrol acetate, trenbolone acetate and zeranol) in humans is, to my knowledge, not known. Whilst it is likely that it will be less than 100% there is no specific information available. However, it should be noted that in the risk assessment of these hormones by JECFA, the risk characterization involved comparison of the theoretical maximum daily intake with the ADI. No correction was made for bioavailability. Hence, the situation is likely to be similar to that for the natural hormones, in that changes in bioavailability from the normal value would change the margin of safety.

Dr. Guttenplan

352. Bioavailability is defined as the fraction of a chemical that enters the general circulation by oral administration compared with that entering the circulation by iv. Injection.

353. Presumably, only the bioavailable chemical can produce adverse (or any) effects, thus in terms of risk assessment, only the portion of the dose of chemical that is bioavailable is significant. *(Toxicokinetics in the National Toxicology Program. NIDA Research Monograph. 173:273-304, 1997.)*

354. The US and Canada maintain that orally ingested estradiol (the major potentially harmful hormone) is essentially inactive, because of poor bioavailability.

355. The US states (para. 41, US rebut. Sub.) "The EC also asserts that the U.S. argument that estradiol 17β is generally inactive when given orally, while "well known", is "still controversial and not consensually accepted by the scientific community." To the contrary, estradiol's low oral bioavailability has found international support in Codex and JECFA ("[i]n general, estradiol 17β is inactive when given orally because it is inactivated in the gastrointestinal tract and liver"), as well as support within the EC from the CVMP, which noted that "the *bioavailability of 17β-oestradiol* esters after oral administration *is low (3% as unchanged oestradiol)*, but might be higher if estrone, an estrogenic metabolite, is included." Also, included is a reference that in a cell culture model (immortalized human intestinal cells (Caco-2 cells)) estrogen does not enter the cell although the estradiol convertible metabolite was detected in the cells. The US states that this supports the hypothesis that estradiol cannot cross the intestinal wall. This latter finding seems paradoxical, because somehow estradiol was converted to estrone, so it must have entered the cell.

356. On the other hand the EC maintains (EC Rebut, para 123) that "recent developments put in doubt the findings of the 1999 JECFA report concerns the bioavailability of residues of these hormones. The 1999 and 2002 SCVPH reports have found that data on which JECFA based its findings are incorrect or insufficient." For instance, "Metabolic studies of orally administered 17ß-oestradiol indicate that as much as 20 percent of a 2 mg dose of micronized E2 is absorbed, with a serum half-life in the range of 2 to 16 hours (Zimmermann et al., 1998; Vree and Timmer, 1988: Ginsburg et al., 1998) and in it is stated that the above reports indicate, the bioavailability of fine-particle 17β-oestradiol administered orally was determined to be 5% compared to a dose administered intravenously. It is also pointed out (EC Rebut, para 124) lipoidal esters (metabolites of estradiol) have high bioavailability and may accumulate in adipose tissue. No data accompany the accumulation hypothesis, although it seems reasonable.

357. It appears that the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account. (Estrone is readily inter- convertible with estrogen). Calculations are presented in the above reference that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children (EC Rebut, para 122). This would represent a risk factor (EC Rebut, para 122).

(f) Good veterinary practice (GVP)

44. Please define "good veterinary practice" (GVP) and/or "good practice in the use of veterinary drugs" (GPVD). What are the relevant Codex standards, guidelines or recommendations relating to GVP/GPVD? Please comment on the statement by the European Communities that the definition of the GPVD is "circular and hence problematic." [see para. 88 of the EC Replies to Panel Questions]

Dr. Boisseau

358. There are several definitions for the good veterinary practice (GVP) and the following one adopted by Codex is satisfactory : " GVP in the use of veterinary drugs is the officially recommended or authorized usage, including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions "

359. Nevertheless, to my knowledge, the Codex Commission has only adopted, in July 2005, a guideline on GVP intended to minimize and put under control the microbial resistance. It did not adopt any guideline on GVP aimed at minimizing the occurrence of veterinary drug residues in animal derived food.

360. The comment of the Europan Communties about GVP is not clear. I suppose that the European Communities means that the conditions of used of veterinary drugs, even officially approved, may differ in a very significant way from one country to another one.

Dr. De Brabander

361. Most probably, several definitions could be found for defining GVP. Hereunder I give one of the Veterinarians of Europe:

Federation of Veterinarians of Europe: Code of good veterinary practice

Veterinarians play an important role in protecting animal welfare, animal health, public health as well as the environment and provide a wide range of services.

This Code of Good Veterinary Practice is a standard specifying the European veterinary ethics and principles of conduct as well as the requirements relating to the quality management system within a veterinary organisation, when the latter:

1. Wishes to improve its ability to give services in conformity with:

- *The legislation in force,*
- *The Professional Code of Conduct in force,*
- *The requirements of the clients,*
- *The ethics principles relating to the services provided and/or the animals under its care.*

2. Must demonstrate its ability to deliver services, which are constantly in line with customer requirements and the legislation in force.

362. A selection of paragraphs on Public Health and the environment is also given below:

2. G Veterinarians and Public Health

- *Veterinarians shall seek to ensure the best protection of public health.*

- *Veterinarians shall, whenever appropriate, advise their customers about measures to minimise the risk of exposure to zoonotic agents, food borne pathogens, residues, contaminants (biological and chemical agents) and antimicrobial resistance.*
- *Veterinarians shall make animal owners aware of their responsibilities to the public.*

2. H Veterinarians and the Environment

- *Veterinarians shall attempt to reduce pollution of the environment by waste avoidance, recycling, using re-usable articles when appropriate, and correct disposal of waste.*

- *Veterinarians shall endeavour to reduce environmental pollution by careful and appropriate use of disinfectants, medicinal products and other chemicals.*

- *Veterinarians shall aim to be environmentally responsible by the economical use of energy and water.*

- *Veterinarians shall organise facilities for separate collection of different types of waste so that they can be sent to the appropriate recycling points.*

- *Veterinarians shall encourage customers to dispose of veterinary waste in a safe manner.*

363. This selection illustrates the importance of the veterinarians in reduction of pollution of the environment and the link between residue analysis and environmental sciences. This applies also to the use of hormones

364. Good practice in the use of veterinary drugs (GPVD), *as defined by the CCRVDF, is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions* (*document: Recommended international code of practice for control of the use of veterinary drugs cac/rcp 38-1993 ; cxp_038e).*

365. The statement by the European Communities that the definition of the GPVD is "**somewhat** circular and hence problematic" refers to the fact that the national authorities have a large impact on this so-called international standard and can influence the application of it.

366. Neither GVP neither GPVD will reduce the risk of "using hormones" for several reasons. Also education plays an important role. Two years ago we had some American students in veterinary medicine in an exchange program: their knowledge of "hormones" their use in the USA and the risks involved was almost zero.

45. In conducting a risk assessment of specific veterinary drugs, what assumptions are made concerning GVP, if any? How, if at all, are risks that might arise from the failure to follow good veterinary practice in the administration of veterinary drugs addressed?

Dr. Boisseau

367. Residue data considered by all the committees such as JECFA, CVMP etc… conducting risk assessments of veterinary drugs are always obtained from studies in which veterinary drugs under review have been admnistered to the target food producing animals according to the officially approved conditions of use of these veterinary drugs. Therefore, MRLs adopted by Codex are only meaningful in countries where GVP are effectively implemented. In addition, it would not be appropriate for the risk assessors to address the case where the veterinary drugs under review could not be used in practice according to the GVPs. It would not be appropriate because it would not be possible for the risk assessors to identify all the possible misuses/abuses and to get the residue data derived from these misuses/abuses. It would not be appropriate also because it would not be ethical for the case where such data, being available, would lead to the conclusion of the risk assessment that,

given a possibly wide margin of safety for a veterinary drug under review, the excess intake of residues associated with these misuses/abuses does not raise any problem of public health. That would encourage all theses misuses/abuses. Therefore, this issue of GVP, misuses/abuses must be taken into consideration not by the risk assessors but by the risk managers.

Dr. De Brabander

368. In conducting a risk assessment of specific veterinary drugs, it is assummed that GVP is followed. However can this be guaranteed?

369. In "A Primer on Beef Hormones" Date : 02/26/99 *text released by the U.S. Interagency Task Force on Beef Hormones.* the following could be read:

> *"Furthermore, the prescribed dosage is the level which produces the maximum economic response in the animal -- the law of diminishing returns -- so that there is no economic incentive for a farmer to use additional implants. A U.S. control system ensures that animals taken to slaughter have normal hormone levels. Thus, farmers have no incentive, economic or otherwise, to misuse the implants."*

370. However, arround the same date studies could be found on the use of Zilpaterol (a powerful beta-agonist of the 3th generation) on top of revalor (both control animals and test animals are implanted with revalor). This illustrates that farmers (and vets) have indeed economic incentives to misuse growth promoting substances (implants or others).

371. I am not aware of any study on public health of the combination of zilpaterol with the substances in revalor. Are the animals of this experiment destroyed?

372. Proceedings, Western Section, American Society of Animal Science Vol. 50, 1999 INFLUENCE OF THE beta-AGONIST, ZILPATEROL, ON GROWTH PERFORMANCE AND CARCASS CHARACTERISTICS OF FEEDLOT STEERS

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ABSTRACT: One hundred forty crossbred steers (373 kg) were used in a randomized complete block design experiment (14 pens, 10 steers/pen) to evaluate the influence of supplementation of a steam-rolled wheat-based finishing diet with 6 mg/kg (as-fed basis) zilpaterol during the final 6 weeks of the finishing period on growth performance and carcass characteristics. Supplemental zilpaterol did not influence (P > .20) DM intake (8.55 vs 8.45 kg/d), but enhanced (P < .01) ADG (27%, 1.42 vs 1.94 kg/d), and feed efficiency (28%, 6.08 vs 4.37). Based on observed NE intake, ADG of the non-supplemented steers was 99% of expected. In contrast, with zilpaterol supplemented steers ADG was 29% greater (P < .01)

Experimental Procedure:
One hundred and forty crossbreed yearlings steers (373 kg) were used in a 42-d finishing trial. Steers were blocked by weight and randomly assigned, within weight groupings, to 14 pens (10 steers/pen). Pens were 510 m with 64 m overhead shade, automatic waterers, and 17 m fence-line feed bunks. The trial was initiated July 22, 1997. Treatments consisted of a steam-flaked wheat-based finishing diet (Table 1) supplemented (as fed basis) with 0 or 6 mg/kg zilpaterol (Zilmax , Hoechst Roussel Vet, D.F., Mexico). Steers were implanted with Revalor (Hoechst Roussel Vet, D.F., Mexico) upon initiation of the trial. Steers were allowed ad libitum access to experimental diets.

46. To what extent were risks from misuse or abuse assessed by JECFA in its evaluation of the hormones at issue? In terms of the three synthetic hormones at issue, how is GVP relevant to the establishment of MRLs by JECFA?

Dr. Boisseau

373. My reply to question 45 above applies also to this question. It covers also the three synthetic hormones which do not raise any specific problem in this domain.

Dr. Boobis

Assessment of risks from misuse and abuse by JECFA

374. Where the conclusion of a risk assessment is such that it is considered appropriate to establish an ADI to protect health (i.e. the critical effects exhibit a threshold), no consideration is given to the likely levels of exposure. The ADI is driven entirely by the toxicology and other relevant biological effects of the substance, which determine the point of departure (usually the NOAEL), and an appropriate uncertainty (or safety) factor. The uncertainty factor used has to account for any inter-species extrapolation, interindividual differences, sensitive sub-populations, absence of a NOAEL and any non-critical gaps in the database (see my reply to question 8 above). In establishing MRLs (relevant here only for the three synthetic hormones), the appropriate residues studies are those obtained after the normal use of the hormones, i.e. in accordance with GVP. This is the policy of all agencies and organisations involved in such activities *(EEC, 1990; EMEA, 2005; FAO, 2006)* (see response to question 62 below under "Multiple implanting, multiple dosing"). The point at which misuse and abuse are relevant in the risk assessment is at the risk characterisation stage, when potential exposure is compared with the ADI. Hence, whilst the TMDI is estimated following use of the hormones according to GVP, it would also be possible to consider other exposure scenarios, in which the hormones were misused or abused. Where exposure exceeded the ADI, the toxicological implications of this would depend on a number of factors (see response to question 62 below). These are as follows:

- The likelihood of violations or off-label use
- The residue levels occurring after such misuse or abuse
- The extent to which exposure to such residues will result in an exceedance of the ADI
- The likely frequency or period over which the ADI will be exceeded
- The acute consequences of exceeding the ADI
- The severity of the endpoint upon which the ADI is based
- The steepness of the dose-response curve for the endpoint upon which the ADI is based

375. JECFA did consider misuse of zeranol when it was evaluated in 1988 *(JECFA, 1988b)*. JECFA gave some consideration of the effects of doses of up to 20 times those approved for the use of MGA on residue levels *(JECFA, 2000a)*. JECFA does not appear to have explicitly considered misuse or abuse of trenbolone. The implications of misuse and abuse of these hormones for human health are considered below (question 62). There would have been no implications for the MRLs recommended. It would have been a decision of Codex as to how it would deal with any exceedances of the ADIs as a consequence of misuse or abuse, as this involves risk management decisions.

EEC (1990). Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin. OJ L 224, 18.8.1990, p. 1–8

FAO (2006). Updating the Principles and Methods of Risk Assessment: MRLs for Pesticides and Veterinary Drugs, Rome Italy (http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/bilthoven_2005.pdf)

JECFA (1988b). Residues of some veterinary drugs in foods and animals, Vol. 41/1, FAO, Rome, Italy

Dr. De Brabander

376. Up to my knowledge, risks from misuse or abuse are not assessed (even denied) by JECFA in its evaluation of the hormones at issue. As was illustrated by the example of the experiments with Zilpaterol (question 45), GVP is very relevant to the establishment of MRLs by JECFA. If other substances (like zilpaterol or ZMA etc…) or incorrect use of implants are used the principle of the establishment of MRLs by JECFA is certainly unvalid.

47. How significant are any differences in GVP in the European Communities, the United States, and Canada? Does the EC risk assessment take into account relevant control mechanisms with respect to GVP in place in the United States and/or Canada? If so, what are their conclusions?

Dr. Boisseau

377. In my e-mail of 26/04/06, I have indicated that I did not think that I am in the position to answer this question. Nevertheless, I think that, as far as growth promoters are concerned, the main problem for the European Communities is that these products are, in the USA and Canada, sold over the counter without any veterinary prescription.

378. As, as it has already been said, the European Communities did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the European Communities took into account relevant control mechanisms with respect to GVPs in place in the USA and/or Canada.

Dr. De Brabander

379. The interpretation of the rules of GVP can be different from country to country. Concerning the dispute on hormones THE difference is of course that in Europe the use of hormones as production aids is not allowed (and thus not included in GVP).

380. As to the relevant control mechanisms with respect to GVP in place in the United States and/or Canada: any control mechanism, that is only based on audits and paper work will not prevent farmers to use either uncorrect use of legal production aids either the use of other illegal growth promotors which are readily available in the US and Canada through the internet.

381. An example: on 2006-17 April 21, 2006 (thus very recently) Health Canada advises consumers not to use unauthorized products containing anabolic steroids. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_17_e.html

382. OTTAWA - Health Canada is advising consumers not to use five products containing illegal anabolic steroids, as they can potentially cause serious health issues such as liver disorders and heart problems. The five products are: Anabolic Xtreme Superdrol, Methyl-1-P, Ergomax LMG, Prostanozol and FiniGenX Magnum Liquid. They are not authorized for sale in Canada as either drugs or natural health products. Canadians using any of these products or any other supplements containing anabolic steroids are advised to stop taking these products immediately and consult with a health care professional.

383. All these products are available through the Internet, maybe mostly for use in bodybuilding but they can also be used in cattle fattening.

384. Are there methods and laboratories to control the abuse of these substances in the US and Canada?

385. Note that "Health Canada" (correctly) recognises the danger of these substances.

48. To what extent does the scientific evidence referred to by the European Communities assess risks to human health from residues of misplaced implants or improper administration, i.e. when administered differently than indicated on the label of the manufacturer or contrary to GVP, of any of the six hormones? Would your reply have been different at the time of adoption of the EC Directive in September 2003? What are the potential hazards, if any, to human health of the use of large quantities, or doses higher than recommended, of any of the six hormones in dispute?

Dr. Boisseau

386. Once again, the reply given to the question No 45 applies also to this question. The outcome of a risk assessment of veterinary drug residues, including the six hormones at issue, cannot apply in the case of misuse/abuse such as use of dosages higher than those approved, use of not approved combinations, repeated administrations, deep intramuscular injections instead of implantation of pellets etc…In this respect, the European Communities is right to state that, in case of these different misuses/abuses, the exposure of consumers may be totally different. Once again, this situation is not specifc to hormones as it applies also to all the veterinary drugs already assessed by JECFA, EU, USA or anywhere else in the world.

387. Having said that, as the European Communities did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses.

388. My reply would not have been different at the time of adoption of the EC directive in September 2003.

389. ADIs are established in order to prevent the toxicological/physiological effects, associated with the corresponding NOAEL, to occur. In case of misuses/abuses, the exposure of consumers to residues may increase to such an extent that the intake of these residues may exceed the established ADI and the toxicological/physiological effects intended to be avoided may occur.

Dr. Boobis

Assessment of risk to human health from misuse or abuse of the hormones in the scientific evidence referred to by the EC

390. The evidence itself is discussed in detail under question 62 below. There was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies. Indeed, the SCVPH (2002) simply noted that "Therefore, these data have to be considered in any quantitative exposure assessment exercise", without undertaking such an exercise. However, it should perhaps be pointed out that the EC had previously taken the view that there was no threshold for some of the critical effects of the hormones and that it was therefore not appropriate to conduct a quantitative risk assessment *(SCVPH, 1999)*. The SCVPH did not change their view on this in their 2002 evaluation of the new information.

391. My reply would not have been different at the time of adoption of the EC directive in September, 2003.

392. In my view, the potential hazards from the use of large quantities of the six hormones in dispute are those dependent on their endocrine activity, including cancer in hormonally responsive tissues. However, I should stress that this is their potential hazard. The potential risk, i.e. the probability that effects would occur, would depend on a number of factors. These include the magnitude of the exposure, the duration of the exposure and the life stage of the exposed individual. From the range of exposures likely from anticipated misuse or abuse the risks are likely to be very low (see question 62).

Dr. De Brabander

393. The answer to this question is already given in question 47. Improper administration of implants or misplaced implants create potential hazards to human health. Moreover, as already mentioned the potential hazards to human health are not the only factor in the debate of the use of hormones as production aids. There are also:

- animal welfare: how do animals feel at improper administration of implants or misplaced implants?
- the environment: excretion of an excess of hormones at improper administration of implants or misplaced implants disturbs the hormonal balance in surface water.
- transformation of hormones: enzymatic reactions are equilibrium reactions (the enzyme is just a catalyst for the reaction); excess of hormones can drive a enzymatic reaction in another direction (e.g. formation of boldenone out of testosterone). Little is still known about this phenomenon.

394. If my reply would have be different at the time of adoption of the EC Directive in September 2003 is a difficult question. Fact is that my reply now is certainly different: more and more scientific data sustain the ban on the use of hormones: the economical profits resulting from using hormones do not balance the potential danger in all of its aspects.

49. What analytical methods, or other technical means, for residue detection in tissues exist to control the use of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice? What tools are available to control the use by farmers of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice?

Dr. De Brabander

395. There are a large number of analytical methods available to control the use of the six hormones in dispute for growth promotion purposes. New methods are regularly presented in international conferences and in the open literature. In Europe a system of community reference (CRL) and national reference laboratories (NRL) is installed so that the analysis carried out by the field laboratories are kept up to the standards of the moment. If necessary I can provide the panel with a large number of methods but I don't think that is the purpose.

396. To control the use by farmers of the six hormones in dispute for growth promotion purposes a number of tools can be used:

- Analysis for legal and illegal hormones in urine, faeces, hair, animal feed and drinking water.
- Audit of the farms on the presence of legal and illegal substances in all kind of formulations.
- Control of the weight gain of the animals in the farm in comparison with normal weigth gains.
- Inspection of the herd on certain symptoms (e.g. hypothyreosis).
- Inspection of the animals at slaughter (e.g. for injection sites).

50. Are there other measures available to the European Communities (other than a complete ban) which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

Dr. Boisseau

397. In my e-mail of 26/04/06, I have indicated that I did not think that I am in the position to answer this question.

398. Nevertheless, I would like to say that, in a given country, the implementation of GVPs and the elimination of misuses/abuses of veterinary drugs must be the responsability of the official authorities of this country which should be able to demonstrate that (1) veterinary drugs are effectively used in compliance with GVP, (2) veterinary drugs associated with sensitive public health issues are used under veterinary control, (3) the official controls, including surveillance of residues, of the implementation of these GVPs are efficient. In the case where it can be established that an exportating country is not in the situation to guarantee that veterinary drugs are effectively used in compliance with GVP, any importating country should have the freedom to take any appropriate measure likely to protect the health of its population. Ban is the last possible measure if all the other options have failed or have been proved ineffective. In the case of hormonal growth promoters, due to the temptation for the farmers to use these products in a way different from the approved ones in order to expect some more economical profit, a agreement should be made between an exporting and an importing country about the content of GVP regarding the use of these products, including a possible involvement of veterinary supervision/prescription and an appropriate scheme of residue surveillance. In addition, if legally authorised and technically feasible, an appropriate information of the consumers of the importating country through a clear labelling could be considered as there is nowadays an increasing demand from consumers about the tracking of food with an informative labelling even concerning legally approved food additives.

399. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Dr. De Brabander

400. To my knowledge, there are no other measures possible to the European Communities, other than a complete ban, which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes.

401. My reply now is even stricter than it would have been at the time of adoption of the EC Directive in September 2003.

51. Does the material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada call into question the potential

applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada?

Dr. Boisseau

402. The replies given to the questions No 45 and 48 apply also to this question.

Dr. De Brabander

403. The material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada calls indeed into question the potential applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada. Since the "older" experiments on which the MRLs (for the 3 synthetic hormones) and the ADIs (for the 3 natural hormones) are based, the scientific knowledge on residues, their link with animal welfare and the impact on the environment has increased considerably. These items are already discussed in the answers on other questions and show clearly that the economical profit of using hormones as production aids doesn't balance the present and potential hazards. Moreover, most consumers aren't prepared to take this risk.

404. Regularly new findings on the residue domain are published. As example, the findings in our own laboratory with maggots of *Lucilia Sericata,* a blowfly. We were able to demonstrate that maggots of *Lucilia Sericata,* when exposed to the hormone are able to convert testosterone into boldenone (2.2 %), boldione (or ADD, 1 %) and AED (15 %).

Boldenone formation by maggots of Lucilia Sericata K. Verheyden, H. Noppe, J. Vercruyss , E. Claerebout, V. Mortier, C.R. Janssen, H.F. De Brabander Anal. Chim Acta 2006, submitted

405. This is only one example of a number of still unknown reactions and illustrates that it is dangerous to introduce substances which may disturb the equilibrium of enzymatic reactions in the body of an animal or a human being (in this case equilibrium of hormones). I have serious doubts that in all the "old" studies which have lead to the establishment of ADI's and MRL's for these substances, these and analogous reactions are taken into account and for instance boldenone en ADD are measured.

[For questions on GVP see the SCVPH Opinions in Exhibits US-1,4, and 17, para.125-127 of EC Rebuttal Submission (US case), paras. 107-109 of EC Rebuttal Submission (Canada case), para. 154 of EC Replies to Panel Questions, Exhibits EC-12, 67, 68, 69, 70, 73, 96, 102, 103, paras. 32 and 54-65 of US Rebuttal Submission, para. 75 of US First Submission, paras. 107-111 of Canada Rebuttal Submission, page 40 of Exhibit CDA-27]

(g) Other

52. Do the risk assessment of the European Communities or any other scientific materials referred to by the European Communities demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes? If yes, why? If not, what kind of evidence would be required to demonstrate such potential adverse affects? Would your response have been different at the time of adoption of the Directive in September 2003?

Dr. Boisseau

406. As already said in the reply to the question No 16, the European Communities did not carry out, strictly speaking, a risk assessment but provided scientific data and hypothesis supporting its worries regarding the safety of these six hormones for human health. Therefore, the European Communities concluded that, given the genotoxic potential of oestradiol-17β, it is not possible to accept any excess intake of residues of this hormone as they are likely to raise a problem of health for consumers and that the available data for the five other hormones were not sufficient to carried out a risk assssment. For the three natural hormones, the European Communities should have integrated in its risk assessment the exposure of consumers to these hormones resulting from the consumption of hormone residues from animals which have not been treated by hormonal growth promoters and the from the daily production of these hormones by humans. So, to my view, the European Communities did not demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth promotion purposes. The kind of evidence required to demonstrate such potential adverse effects should be (1) toxicological data indicating that the values of the ADIs established by JECFA are not conservative enough, (2) data on residues in treated/non treated cattle and on daily production of hormones in sensitive individuals indicating that the hormonal residue intake associated with the consumption of meat from treated cattle is such that the established ADIs would be exceeded in the case of use of growth promoters.

407. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Dr. Boobis

Risk to humans from consumption of meat from animals treated with growth promoting hormones

408. This is a complex question to address. A risk assessment involves some interpretation of data. For example, whether an effect is compound-related, whether an effect is adverse, the location of any threshold, whether effects seen in vitro are apparent in vivo, whether associations reported in epidemiological studies might be subject to bias or confounding *(IPCS: EHC 70, 1987 and EHC 104, 1990; WHO, 1996 and 2001)*. Hence, whether a risk assessment demonstrates that a potential for adverse effects on human health arises from consumption of meat from cattle treated with any of the six hormones in dispute depends on those conducting the risk assessment. However, whether the scientific information on which this risk assessment was based, or any other materials referred to by the EC demonstrate such potential is another question. In my view, none of information provided by the EC demonstrates the potential for adverse effects in humans of any of the six hormones in meat from cattle in which they are used for growth promotion purposes at the levels to which those consuming such meat would be exposed. The studies on genotoxicity provide no convincing evidence of potential for harm in consumers. The weight of evidence is that the hormones are not genotoxic in vivo even at doses well above those that would be present in meat from treated cattle. The carcinogenic effects observed are entirely consistent with a hormonal mode of action that exhibits a threshold that would be well above the intake arising from consumption of meat from treated cattle. Other effects of the hormones that have been observed either in experimental animals or in exposed subjects occur at doses much higher than those to which consumers would be exposed via meat from treated cattle. As such, there would be no risk of such effects in humans from such exposures. There is much debate about the possible endocrine effects of low dose exposures to hormones such as oestradiol. However, all of the major reviews in this topic have concluded that whilst there are data gaps, there is no evidence that low level exposure is causing harmful effects in humans.

409. "Analysis of the human data by itself, while generating concerns, has so far failed to provide firm evidence of direct causal associations between low-level (i.e., levels measured in the general population) exposure to chemicals with EDCs and adverse health outcomes" *(Damstra et al, 2002)*

Damstra, T., Barlow, S., Bergman, A., Kavlock, R., and Van der Kraak, G. (2002). Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO publication no. WHO/PCS/EDC/02.2. World Health Organization, Geneva, Switzerland.

410. "However, it is somewhat reassuring that after substantial research in the past decade, there have been no conclusive findings of low-level environmental exposures to EASs [endocrine active substances] causing human disease" *(Miyamoto and Burger, 2003).*

411. The question on what sort of evidence would be required to demonstrate such potential adverse effects presupposes that they are demonstrable. In order to demonstrate whether or not such effects occur it would be necessary to conduct studies of human systemic exposure from consumption of meat from treated cattle. Such studies would require very sensitive analytical methods, capable of establishing whether there is any change in circulating hormone levels in the first place. Studies would need to be carried out in relevant sub-populations, such as prepubertal males. Epidemiological studies, in which both exposure and outcome are carefully assessed would also be necessary. However, it should be emphasised that on the basis of the information available, I would rate the risk of adverse effects in humans consuming meat from treated cattle as minimal.

412. My response to this question would have been the same at the time of adoption of the EU Directive in September 2003.

Dr. Guttenplan

413. Calculations are presented (EC Rebut, para 122) that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen exceeding the daily production rate of oestradiol in pre-pubertal children (EC Rebut, para 122). Although the US and Canada question the accuracy of the assay originally employed for estrogens at the low levels found in children, recent reports (Wang, S., Paris, F., Sultan, C. S., Song, R. X., Demers, L. M., Sundaram, B., Settlage, J., Ohorodnik, S., and Santen, R. J. Recombinant cell ultrasensitive bioassay for measurement of estrogens in postmenopausal women. J Clin Endocrinol Metab, *90:* 1407-1413, 2005 and references therein), indicate that more recently reported levels used by the EC are accurate. In addition, levels in post-menopausal women were also very low. However, other approximations are used in that calculation. For pre-pubertal children, even with the low bioavailabilty of estrogen along with and its low levels in meats, it appears possible that intake levels would be within an order of magnitude of those of the daily production rate. This is greater than FDA's ADI and suggests some risk to this population. If there genotoxic effects of estradiol in children, they may be reflected over a lifetime, as mutations arising from DNA damage are permanent. It seems the more accurate methods of analysis could now be used to measure the effect of eating hormone-treated beef on blood levels of estrogen in children and post-menopausal women. If practical, this experiment would be important in establishing or refuting the arguments of the EC.

414. My response would have been more uncertain in 2003, because the assay for serum levels of estrogens was less validated then.

53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations? Would the systematic use of these and the synthetic hormones in combination have any implications on how the scientific experiments and the risk assessments are to be carried

out? If so, have the scientific materials referred to by the European Communities or relevant JECFA reports taken into account the possible synergistic effects of such combinations on human health? [see sections 4.2-4.3 of the Opinion of the SCVPH of 2002 in US Exhibit 1]

Dr. Boisseau

415. It is true, as it is written in the section 4.3. of the 2002 Opinion of SCVPH, that the data about genotoxicity of hormones have obtained from tests conducted only with individual substances as it has been always the case for all the toxicity studies considered everywhere in the risk assessment of veterinary drug residues. Considering that it has been established that progesterone and testosterone are not genotoxic, it is not likely that the testing of combinations of progesterone or testosterone with oestradiol-17β would have led to synergistic effects compared with those obtained from these individual substances.

Dr. Guttenplan

416. From the data presented, it is true that progesterone and testosterone are used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations (sections 4.2-4.3 of the Opinion of the SCVPH of 2002).

417. In principle the use of mixtures should complicate risk assessments/scientific experiments, as they would have to evaluate/investigate each component alone and in combination. This is a major undertaking as effects of individual agents may be additive, inhibitory, and synergistic or there may no effect. It appears from the evidence submitted that, by far, estrogen is the major agent of risk and because the concentrations of all of the hormones in beef are so low, that they would be unlikely to affect the potency of estrogen. However, it appears that no experiments on effects of combinations were performed, so some uncertainty exists there.

54. What is the acceptable level of risk reflected in the Codex standards for the five hormones at issue? How does this compare to the European Communities' stated objective of "no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion". [see para. 149 of EC Rebuttal Submission (US case)]

Dr. Boisseau

418. The acceptable level of risk reflected in the Codex standards for the five hormones at issue is, as for all the other substances already assessed, expressed by the ADIs established for these substances. The spirit of the risk assessment procedure adopted by the Codex and implemented by JECFA is that the amount of residues expressed by an ADI represents the quantity of these residues which can be ingested daily by consumers over life time without causing any problem of health. This approach is obviously different from the European Communities' stated objective of "no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion" which implies, to be reached, that these five hormones should not be used. The idea supporting this statement is probably that growth promoters raise a specific problem regarding the benefit/risk assessment associated with their use. In the case of veterinary drugs used for therapy, the risk is expressed in term of human health and the benefit in terms of animal health and that can be considered as ethical. For the growth promoters, the benefit is "only" economical and for this reason, the European Communities may not accept any risk, even theoritical, resulting from the use of these growth promoters only intended to increase economical profits.

Dr. Boobis

Acceptable level of risk

419. The Codex standards for the hormones at issue represent "no appreciable risk with daily exposure over a lifetime" (Definition of ADI by WHO, 1996, 2001 and CVMP, 2005). This is based on the JECFA conclusion that all of the potentially adverse effects of the hormones have thresholds. By using a NOAEL or surrogate if necessary, such as the LOAEL, and appropriate uncertainty (or safety) factors, a level of exposure is determined up to which the risk is considered minimal, i.e. the ADI (see my replies to questions 7-12 above). The level of any residual risk has never been quantified but is considered to be acceptable to society. The Codex standard is equivalent to the EC's stated objective of "no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion", and indeed is the dame as the CVMPs (2005) definition of ADI. This is because the EC uses the same risk assessment paradigm as JECFA for establishing ADIs and hence if the data are interpreted in the same way there should be no difference in the level of risk identified in the risk assessment. From a scientific perspective, the difference arises from differences in the way that the data are interpreted and in particular whether or not it is concluded that there is a threshold for the effects of concern.

420. However, the distinction between risk assessment and risk management must be stressed (see my reply to question 5 above). Whether to invoke the precautionary principle is a risk management decision. It is beyond the scope of my responses to go into this in detail. One input to risk management decisions is the output of the risk assessment, part of which is an evaluation of the uncertainty associated with that output. Risk management has to weigh the risk assessment and a number of other factors in reaching a conclusion. Hence, the issue is in part not so much the level of risk that is acceptable, but the level of concern should the risk estimates be incorrect.

Dr. Guttenplan

421. Codex has set ADI's for the hormones (except MGA, which, I couldn't locate) but states that MRL's are not necessary as meat from animals maintained with good animal husbandry practices would not be likely to pose a threat to human health (CDA 22, Codex list of standards). This is not in accord with the EC's stated objective. The EC maintains that for estrogen and possibly the other hormones, some potential risk exists. The question of what level of risk has not been addressed by the EC.

55. Do the Opinions of the European Communities or other scientific materials referred to by the European Communities evaluate the extent to which residues of growth promoting hormones in meat contribute to what the European Communities calls "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings"? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 151 of EC Replies to Panel Questions, paras. 43-44 of US Rebuttal Submission, paras. 83-85 of Canada's Rebuttal Submission]

Dr. Boisseau

422. The European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute to "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings". Besides the European Communities recognizes that in saying, in the para 151 of its reply to Panel questions that " it is not so much necessary to compare (if

it is only possible) the two situations (residues of hormones in meat from cattle not treated with growth-promoting hormones and residues in meat from cattle treated with growth-promoting hormones) and then try to quantify how much one is more risky than the other one". Therefore, it can be thought that the position of the European Communities is a position of principle. This position is inflenced by risk management considerations and by the implementation of the so called precautionary principle.

423. My reply would not have been different at the time of adoption of the EC Directive in September 2003.

Dr. Boobis

Additive risks

424. Two different issues are represented here. One is so-called aggregate risk. This has been defined as "the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance" *(US EPA, 2001*). Hence, at issue is the extent to which exposure to the natural hormones present in meat from treated cattle aggregates with endogenous levels of the same hormone, and exposure to that hormone from any other source, such as in the form of a therapeutic agent.

425. The second is cumulative risk. This has been defined as "the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a group of substance sharing a common mechanism of toxicity" *(US EPA, 2001)*. Here, the issue is the extent to which compounds with similar effects should be cumulated, with each other and with other similar substances of either exogenous or endogenous origin.

> *US EPA Office of Pesticide Programs (2001). General Principles For Performing Aggregate Exposure And Risk Assessments (http://www.epa.gov/pesticides/trac/science/aggregate.pdf)*

426. The EC Opinions and other materials referred to by the EC do not quantify the extent to which residues of the hormones contribute to aggregate exposures or cumulative exposures to multiple hazards. Aggregate risk where one of the major exposures is from a substance found endogenously, is most common for essential minerals and vitamins. However, here the exposures of concern are mainly exogenous, as for most vitamins and minerals there is no endogenous production *(see SCF, 2000)*. However, there are a few exceptions, such as vitamin D. In this case, the *SCF (2002)* took into account the endogenous production rate in estimating a tolerable upper intake level. An important consideration was the extent to which exogenous exposure changed circulating levels of the active vitamin. This is somewhat analogous to the approach taken by *JECFA (2000b)* for the natural hormones, in that exposure was calibrated against doses that did or did not cause any change in circulating levels of the hormone.

SCF (Scientific Committee on Food) (2000). Guidelines of the for the development of tolerable upper intake levels for vitamins and minerals. SCF/CS/NUT/UPPLEV/11 Final (http://ec.europa.eu/food/fs/sc/scf/out80a_en.pdf)

SCF (Scientific Committee on Food) (2002). Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin D. SCF/CS/NUT/UPPLEV/38 Final (http://ec.europa.eu/food/fs/sc/scf/out157_en.pdf)

427. The issue of cumulative risk is more complex. Indeed, such considerations are currently applied in only very limited circumstances, for example dioxins and organophosphates. Within the EU, no such cumulative risk assessments have been undertaken routinely for any residues of

pesticides or veterinary drugs in food. Indeed, there is currently no agreement as to the appropriate methodology to use *(*see *EC, 2005b)* and such assessments do not appear to be foreseen in the near future for residues of veterinary drugs. Hence, risk assessments are performed on the individual compounds. However, it should be emphasized that any risk assessment group would deal with substances on a case by case basis, and the absence of agreed methodology would not necessarily preclude some consideration of cumulative risk, if this was deemed to be a major and immediate concern.

EC (2005b). Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_070/l_07020050316en00010016.pdf)

428. The importance of both aggregate and cumulative risk would depend critically on whether or not there was a threshold for the dose-response relationship. One of the arguments of the EC is that hormones can cause cancer by a genotoxic mechanism which would have no threshold. If this were true, it is certainly correct that any additional exposure would have an incremental effect on risk, if one assume a linear no-threshold dose-response relationship. This would be the default under such circumstances. The incremental risk would depend on the extent to which the additional exposure from hormones in meat from treated cattle changed the overall exposure, with respect to the endogenous levels present. In contrast, for compounds with the same mechanism of action, if there were a threshold for all of the biological effects of concern, additional exposures would only be of concern when they resulted in a total potency-corrected exposure that was above the threshold (the ADI) *(Silva et al, 2002).*

429. My reply would have been the same at the time of adoption of the EC Directive in September 2003.

*Silva E, Rajapakse N, Kortenkamp A (2002). Something from "nothing"--eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. Environ Sci Technol, **36**:1751-1756*

Dr. Guttenplan

430. In general the EC do not attempt to evaluate "the additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings". However, as described in the answer to question 52, an estimated comparison has been presented of amount of estrogen contributed by consumption of meat from hormone-treated cattle and the amount normally produced in prepubescent children.

431. I am more comfortable with this estimation now, and then I would have been in 2003 because of improved analytical techniques.

56. Has JECFA/Codex considered in its risk assessment of the five hormones such "additive risks? Are there internationally recognized guidelines for conducting assessments of "additive risks"?

Dr. Boisseau

432. JECFA/Codex considered in its risk assessment of the natural hormones such "additive risks" and concluded that, given the wide margin of safety between the maximum estimated intake of residues for the these hormones and the corresponding established ADIs, that there was no risk for consumers' health associated with the estimated ingestion of these residues. JECFA /Codex did not

consider such "additive risks" in its risk assessment of the synthetic hormonal growth promoters. To my knowledge, there is no internationally recognized guidelines for conducting assessment of "additive risks".

Dr. Boobis

Consideration of additive effects by JECFA/Codex

433. JECFA/Codex did consider aggregate risk from exposure to the natural hormones where present as residues in meat from treated cattle. Such exposures were considered to represent a trivial increase in overall exposure to hormonally-active material from other exogenous sources and in particular from endogenous sources *(JECFA, 2000)*. JECFA/Codex did not use formal methodology to assess cumulative risk from exposure to the hormones. However, JECFA did consider that the dose-response curves for potential adverse effects from the hormones all exhibited thresholds and that there was a considerable margin of exposure for all of the hormones between the TMDI and the ADI. Hence, it was concluded that there would be no additional risk over background by exposure to any residues from meat from treated cattle. In a cumulative risk assessment consideration needs to be given to the exposure pattern. It is not appropriate to assume that exposure to each substance will be at the TMDI, as this would require chronic exposure to each hormone at the maximum possible level for all of them. To overcome such compounded conservatism in the evaluation, probabilistic approaches to exposure assessment have been used when performing a cumulative risk assessment *(US EPA, 2002)*

434. JECFA has developed specific methodology for performing a risk assessment of dioxins and related substances that share a common mechanism of action *(JECFA, 2002a)*. *Ad hoc* approaches have been applied to a very limited extent to certain pesticide and veterinary drug combinations, from example when they share a common metabolite. However, there are no agreed international guidelines for conducting a full cumulative risk assessment. One of the difficulties is in obtaining representative consumption data for substances used in food production. Some of the issues involved, and the methodological approaches that have been developed have been reviewed by *Wilkinson et al (2000)*. However, it should be noted that these methodologies are applicable to compounds that share what has been defined as a common mechanism, i.e. there is a cumulative risk. There is no international agreement on how to undertake a combined risk assessment of compounds acting by the carcinogenic mechanisms suggested by the EC for the hormones, i.e. genotoxicity via direct or indirect interaction with DNA. If one were to assume no threshold for the effect, and apply ALARP, it would not be necessary to perform a cumulative risk assessment of such compounds.

JECFA (2002a). Safety Evaluation of Certain Food Additives and Contaminants: Polychlorinated Dibenzodioxins, Polychlorinated Dibenzofurans, and Coplanar Polychlorinated Biphenyls. WHO Food Additives Series: 48, WHO, Geneva

US EPA (2002). Organophosphate Pesticides: Revised Cumulative Risk Assessment (http://www.epa.gov/pesticides/cumulative/rra-op/)

*Wilkinson CF, Christoph GR, Julien E, Kelley JM, Kronenberg J, McCarthy J and Reiss R (2000). Assessing the risks of exposures to multiple chemicals with a common mechanism of toxicity: how to cumulate? Regul Toxicol Pharmacol, **31**:30-43*

Dr. Guttenplan

435. I could find assessment of additive risks of the hormones in the documents, and I not aware of any internationally recognized guidelines.

57. Canada comments that "one single molecule that the European Communities considers so dangerous from meat derived from animals treated with hormone growth promoters is suddenly not at all that dangerous when consumed from meat from animals treated for therapeutic or zootechnical purposes. The European Communities' concern about the genotoxic potential of oestradiol-17β suddenly and inexplicably disappears." To what extent are hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes, taken into account by the European Communities, if at all, in its assessment of the cumulative effects from the consumption of meat containing residues of the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 97 of Canada Rebuttal Submission; paras. 17-20 of US Opening Statement]

Dr. Boisseau

436. The comment of Canada stating that " one single molecule …inexplicably disappears" refers to the theoritical assumption that one single molecule of a genotoxic compound, coming in contact with the human genetic material, could be likely to damage it and therefore to induce a carcinogenic process. This worry supports to some extent the position of the European Communities regarding oestradiol-17β. Therefore, starting from this theoritical and somewhat extreme assumption, Canada challenges the authorization, by the European Communities, of the use of oestradiol-17β for therapeutic and zootechnical purpose. It has to be noted that, according to the directive 2003/74/EC, oestradiol-17β can only be used for three precise therapeutic indications and only until 16/10/2006 for the induction of oestrus. The European Communities thinks that, given the conditions of theses uses of oestradiol-17β (limited number of treated animals, limited use in the life of these animals and very low probability to see these animals slaughtered after treatment), the exposure of consumers to oestradiol-17β residues resulting from these uses can be considered as negligeable. If this EC asssumption can be accepted, it raises nevertheless a problem of principle as it represents an exception regarding the very strict position of EC stating that it is not possible to accept any increase of the exposure of consumers to oestradiol-17β residues. As soon as the European Communities accepts to considers these residues resulting from these therapeutic and zootechnical use of oestradiol-17β as negligeable, it enters in a quantitative, or at least in a semi quantitative, exposure assessment procedure for these oestradiol-17β residues and, starting from that, it has no good reason to object to consider a wider exposure assessment covering all the residues resulting from the different sources of oestradiol-17β. This comment has already been made in my reply to question 31.

437. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Dr. Boobis

Aggregate and cumulative exposure to hormones

438. As indicated above (in my reply to question 56), combined exposures to the same substance from more than one source has been described as aggregate exposure whilst exposure to more than compound acting by the same mechanism has been described as cumulative exposure. To my knowledge no account is taken of hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic purposes, by the EC in its assessment of the aggregate or cumulative effects of the hormones in meat from cattle treated for growth promotion. However, this reply needs some clarification. Firstly, the issue of aggregate and cumulative risk, as indicated above (in my reply to question 56), depends upon assumptions about the nature of the dose-response relationship. Second, though unlikely given the EC's views on the growth promoting hormones, the need for taking into account such other exposures would depend on how far exposure was considered

to be from any threshold, i.e. the margin of exposure. My reply would have been the same at the time of adoption of the EC Directive in September 2003.

Dr. Guttenplan

439. The EC does not really take into account hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes in their risk assessments. Their reasons are summarized in (EC rebut US sub. Para 114). "Exceptions to the ban on meat from hormone-treated cattle were made only for the use of certain of these substances for zootechnical and therapeutic purposes where no viable effective alternatives appeared to exist. This exception was based on the assessment that owing to the nature and limited duration of the treatments, the limited quantities administered and the strict conditions imposed to prevent misuse, that this use did not constitute a hazard for public health." This is a reasonable response. My response would not have been different in 2003.

58. Please comment on the EC statement in para. 94 of the EC Replies to Panel Questions that "the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be", taking into account para. 105 of Canada Rebuttal Submission.

Dr. Boisseau

440. My reply to question 55 applies to this question as well.

Dr. Boobis

Dependency of risk on dose

441. Again, this depends critically upon the conclusion regarding the nature of the dose-response relationship. JECFA has concluded that there was a threshold for all of the potential adverse effects of the hormones and that it was possible to establish ADIs. Hence, as indicated above, exposure below the ADI is considered to be without appreciable risk. Estimated exposure from consumption of meat from treated cattle would result in hormone intakes that were well below the respective ADI's, in the case of oestradiol its intake would represent only 1.5% of the ADI *(JECFA 2000a, b)*. Hence, within quite broad limits, higher exposure would not result in any increase in risk. This would be the case until the ADI was exceeded. It should also be noted that for the critical endpoints of concern in the JECFA evaluation, including cancer, the risk would be significant only with prolonged exposure *(Coombs et al, 2005)*. Hence, occasional exposure even above the ADI would be considered to pose no appreciable risk.

Dr. Guttenplan

442. This is indeed a very weak statement by the EC. However, the alternative would be to suggest a risk that might be wildly inaccurate, due to the limitations imposed by the lack of solid data on levels of hormones in meat. Perhaps a better approach would have been to suggest several scenarios. These could be validated or disproved by subsequent studies.

59. Does the scientific evidence referred to by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see para. 132 of Canada Rebuttal Submission]

Dr. Boisseau

443. The scientific evidence referred to by the European Communities allows to identify adverse effects of hormonally active substances on the immune system. Nevertheless, as these data have not been used by the European Communities to conduct any quantitative risk assessment likely to establish, for these effects associated with the hormonal properties of growth promoters, thresholds and ADIs different from those proposed by JECFA, it is not possible to conclude that this scientific evidence allows to identify any adverse effects on the immune system associated with the consumption of meat from cattle treated with the growth promoters at issue.

444. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Dr. Boobis

Effects on the immune system

445. The evidence on immune effects of hormones such as oestradiol referred to by the EC does not identify any adverse effects on the immune system from consumption of meat from treated cattle. In general, clear evidence for immune effects were observed only at high doses. There is no evidence that doses such as those resulting from consumption of meat from treated animals have any effect on the immune system *(*JECFA, *2000b; CVMP, 1999).* It should also be noted, that in the case of immune effects, exposure relative to endogenous levels is a critical issue. Given the large margin of exposure on anticipated intake from residues in meat from treated animals, no effect on the immune system is anticipated, as immune modulation is dependent on dose and there are thresholds for such effects *(Barton and Clewell, 2000; Kroes et al, 2004).*

446. My reply would not have been different at the tile of adoption of the EC Directive in September 2003.

Barton HA and Clewell HJ 3rd (2000). Evaluating noncancer effects of trichloroethylene: dosimetry, mode of action, and risk assessment. Environ Health Perspect, 108 (Suppl 2):323-334

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG and Wurtzen G; European branch of the International Life Sciences Institute (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol, 42:65-83

Dr. Guttenplan

447. The relationship between estrogen and autoimmune diseases has received considerable attention (Opinion SCVPH, April 30, 1999, section 2.4). There is evidence that estrogens can be involved in Lupus, rheumatoid arthritis, thyroiditis. In addition the development of allergies is thought to be at least partially related to estrogens. The studies in experimental animals also did not identify any immune-related effects, although it is not certain the types of possible effects in humans would be detected in experimental animals. No definitive studies have related intake of meat from hormone-treated animals to the above disorders.

448. My reply would not have been different in 2003.

60. Does the scientific evidence referred to by the European Communities identify and evaluate whether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth

promotion purposes when these hormones are administered as feed additives (MGA) or implanted? Are you aware of any differences?

Dr. Boisseau

449. I do not understand this question as MGA is only used as feed additive and the five other hormones are not used as feed additive. Regarding the exposure assessment, the risk is potentially higher with implanted growth promoters as there are more "options" in terms of misuses/abuses. Nevertheless, to this respect, the scientific evidence referred to by the European Communities does not identify and evaluate wether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives or implanted.

Dr. Boobis

Relevance of method of use of hormones

450. The scientific evidence referred to by the EC does not identify any difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes and when they are administered as feed additives or implanted. I am not aware of any such differences. None would be expected, as in all cases maximum intake would be well below the ADI. However, there is a situation which, at least hypothetically, could give rise to a difference in effects. This would be the misuse or abuse of the compounds when used as growth promoters, giving rise to increased intake because of a misplaced implant or entry into the food chain of tissue containing the implant (i.e. cow's ear). However, whilst this would lead to increased exposures, it is still unlikely this would exceed the ADI, and certainly not for any period of time. It is also an unlikely occurrence in view of the way in which the hormones are used and controlled.

Dr. Guttenplan

451. This question appears not to be specifically addressed, but MGA is the only hormone which might be administered by both methods. The potential for excessive exposure to MGA exists by both routes (oral and implantation), but it cannot be stated and I am not aware of which route is more likely to contribute to high levels in meat (SCVPH, section 4.1.4).

61. In your view and in the light of information provided by the parties as well as the work undertaken at JECFA and Codex, did the the scientific evidence available to the European Communities at the time it adopted its Directive (September 2003) allow it to conduct an assessment (quantitatively or qualitatively) of the potential for adverse effects on human health arising from the consumption of meat from cattle treated with (a) progesterone; (b) testosterone; (c) trenbolone; (d) zeranol; and (e) melengestrol acetate? Would your response differ in light of the scientific evidence provided which is subsequent to the adoption of the Directive?

Dr. Boisseau

452. It is difficult to reply to this question as I don't really know what were the data available to the European Communities at the time it adopted its directive (September 2003). On the other hand, it is always possible to ask for more data in order to clarify more issues so that the willing to eliminate any scientific uncertainty could result in an endless assessment process.

453. My reply would not have differed in light of the scientific evidence provided which is subsequent to the adoption of the EC directive in September 2003.

Dr. Boobis

Availability of data for risk assessment prior to September 2003

454. In my view there was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue (see comments above for details of the basis of this response). My reply would not have been different at the time of adoption of the EC Directive in September 2003.

Dr. Guttenplan

455. The evidence does indicate that potential adverse effects exist for all of the hormones. However, the ability to make a risk assessment (qualitative or qualitative) does vary between compounds.

456. Progesterone, testosterone have been extensively investigated and the assessment seems sound and is based on the no effect level and a safety factor. (JECFA meeting 52, report-WHA TRS 893).

457. There is more limited evidence available for Trenbolone and Zeranol and most of it is *in vitro* (SCVPH 2002 Opinion) or not recent (e.g., JECFA meeting 34th report, 1989 and 32nd report, 1988). However, both appear to be potentially significantly estrogenic. Experimental and analytical methods have improved but it does not appear that accurate ADI's can be established at this point. Studies in experimental animals and studies on levels in beef are still needed. However, from the data available at the time of the Directive, the potential for adverse effects could not be ruled out.

458. Melengestrol acetate. The assessment for melengestrol acetate seems sound. Thorough metabolic and estrogenic studies have been carried out. Actual levels in beef were not provided. (JECFA 62 FNP 41/16).

459. My opinion would not have been different in 2003.

62. Does the scientific evidence relied upon by the European Communities support the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why?

Dr. Boisseau

460. The scientific evidence relied upon by the European Communities has certainly provided new interesting data potentially useful for conducting the risk assessment of growth promoter residues. For all that, these new data do not demonstrate any important gaps, insufficiencies and contradictions in the scientific information used by JECFA for conducting its risk assessments. In order to decide wether or not more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes

can be assessed, it should be necessary to conduct a temporary risk assessment with these new data in order to see to what extent the conclusions of this temporary risk assessment is significantly different from those already performed by JECFA. If it would be the case, it would be necessary, at this time, to identify the additional studies necessary to carry out in order to clarify all the outstanding issues and to complete the risk assessment of the residues of hormones used as growth promoters.

461. My reply would not have been different at the time of adoption of the EC directive in September 2003.

Dr. Boobis

Additional information provided by the studies initiated since 1997

Analytical techniques and bioassays for screening

462. The studies on developing improved analytical methods were considered by the SCVPH (2002) to have been inconclusive.

463. "Despite a number of positive analytical results in this study, the low number of samples does not allow a qualified validation of typical characteristics such as sensitivity, specificity, accuracy and reproducibility (study 1, study 8)." I agree with this conclusion.

464. "The obtained results suggest that the use of recombinant yeast and rainbow trout hepatocytes to detect oestrogenic compounds is not justified in view of their lack of sensitivity" (study 9). I agree with this conclusion. It is of note that despite the use of similar strategies, the limit of sensitivity of the yeast reporter assay used by Le Guevel and Pakdel (2001) in study 9 was substantial less that that of Klein et al (1994).

Bovine metabolism of oestradiol-17 and oestrogenic potency of residues

465. One of the potentially relevant observations was the finding of oestradiol fatty acid esters produced in cattle following treatment (study 3). The study of Hoogenboom et al (2001) showed that the intrinsic oestrogenicity of these esters was much lower than that of oestradiol, by 25-200 fold. Paris et al (2001), have shown that most likely due to kinetic differences, the oestrogenicity of the fatty acid esters in vivo is up to 10-fold greater than that of oestradiol. However, it is apparent that the difference in potency from the parent hormone is not very great or even apparent at low doses, where effects were minimal. Given these findings and that the esters are not the major residue in meat from treated animals, that in some tissues such as muscle, levels are much lower than those of oestradiol (Maume et al, 2001), and that total exposure will be very low (JECFA, 2000), particularly when the balance of the diet is considered, these findings do not raise additional concerns regarding the potential adverse health effects of the hormones when used to treat cattle. An additional point to note is that in all of the studies cited above on the fatty acid esters of oestradiol, concentrations were expressed in units of mass per litre or per kg. However, as only the oestradiol moiety is hormonally active (Hoogenboom et al, 2001), this tends to overestimate potency relative to that of oestradiol by a factor of 2-fold (due to the difference in molecular weight relative to that of oestradiol).

Maume D, Deceuninck Y, Pouponneau K, Paris A, Le Bizec B and Andre F (2001). Assessment of estradiol and its metabolites in meat. APMIS, 109:32-38.

Paris A, Goutal I, Richard J, Becret A and Gueraud F (2001). Uterotrophic effect of a saturated fatty acid 17-ester of estradiol-17beta administered orally to juvenile rats. APMIS, 109:365-375

Multiple implanting, multiple dosing

466. In study 5, the impact of misuse and multiple dosing on residual hormone levels in meat was determined. Dosing at up to 10 times the approved dose, resulted in an increase in the tissue concentrations of some hormones in some tissues to values above the MRL for those hormones for which Codex has established an MRL. For those hormones for which an MRL has not been specified, there were also increases in some tissues (Lange et el, 2001).

467. "Treatment with zeranol and testosterone propionate, even after multiple application, does not cause any problems, as far as infringement of threshold levels is concerned."

468. "Exceeding of the MRL was found in the liver in one out of two animals after 3-fold and in two out of two animals after 10-fold dose of the 200 mg trenbolone acetate-implant". No exceedances were seen in muscle, kidney or fat, even at 10-fold the approved dose.

469. For oestradiol, the maximum increase observed in any tissue was not greater than proportional to the dose applied. Hence, even at 10-fold the approved dose, intake would be well below the ADI. This would be offset by the fact that not all tissues had such elevated levels, and the probability of consuming such high residue levels of a regular basis is minimal. It should also be noted that Codex did not specify an MRL for oestradiol, as it was considered unnecessary.

*Lange IG, Daxenberger A and Meyer HH (2001). Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: effect of the implant preparations Filaplix-H, Raglo, Synovex-H and Synovex Plus. APMIS, **109**:53-65*

470. In the study on misplaced implantation sites (Daxenberger et al, 2000), substantial residual hormone was sometimes found at the implantation site when this was not as recommended. However, for these findings to have significance for the consumer a number of factors need to be considered. These include the likelihood of off-label use of the hormones, the failure to detect the implantation site, the use of the implantation site for food use, the contribution of the contaminated meat to the diet and the frequency of such contamination. No data have been presented on the prevalence of such significant contamination as a consequence of the veterinary use of the hormones. Indeed, no evidence is presented that such misuse does occur with the consequences suggested by the authors.

*Daxenberger A, Lange IG, Meyer K, Meyer HH, Daxenberger A, Lange IG, Meyer K and Meyer HH (2000). Detection of anabolic residues in misplaced implantation sites in cattle. J AOAC Int, **83**:809-819*

471. In studies on MGA (Daxenberger et al, 1999) tissue levels increased with dose, most markedly in fat. Whilst in fat, there was a roughly proportional increase with dose, in other tissues (muscle, kidney, liver) the fold-increase was appreciably less than the fold-increase in dose. Using the values obtained in the study of Daxenberger et al (1999) at 10 times the maximum approved dose, consumption of all four tissues (liver, kidney, fat and muscle) at the JECFA levels (300 g muscle, 100 g liver, 50 g kidney and 50 g fat per day) would result in a slight exceedance of the ADI (2.5 µg cf 1.8 µg). However, it should be noted that this would require all of the tissues to be from animals treated with the high dose, and exposure would have to be over a prolonged period of time. The probability that this would occur is extremely low.

*Daxenberger A, Meyer K, Hageleit M and Meyer HH (1999). Detection of melengestrol acetate residues in plasma and edible tissues of heifers. Vet Q, **21**:154-158*

472. In risk assessment amongst the objectives is to determine whether it is possible to set health based guidance values (e.g. ADI) and upper levels for exposure (reference values or MRLs). If

possible and necessary, such values should be established. MRLs are established following use of the drug according to Good Veterinary Practice (GVP; also Good Practice in the Use of Veterinary Drugs, GPVD). This is the policy of all agencies and organisations involved in such activities *(EEC, 1990; EC, 2005b; FAO, 2006).* An additional question that may be asked is the consequence of abuse or misuse. However, such inappropriate activity cannot be used as the basis for establishing MRLs. This is because whilst use according to GVP can be foreseen and regulated, it is not possible or appropriate to regulate any conceivable misuse or abuse, whether actual or hypothetical. Normally, the risk management strategy to deal with this is to ensure adequate surveillance of residues and to put in place a system of penalties for violation. This is the situation for veterinary drugs in all regions where they are subject to market authorisation, including the EU and the USA. In assessing the risks from abuse or misuse, from a human health perspective, the concern is whether the consequent residues would result in exposure that exceeded the ADI. Exceedance of the MRL or other nominal tolerance level for residues his implications for detecting abuse or misuse in surveillance programmes, but has no direct link with whether there is a health concern or not. For example, residue levels from the use of zeranol according to GVP would result in TMDIs below the ADI. MRLs were established accordingly, so that there is a margin by which the residues can exceed the MRLs, yet intake will still be no greater than the ADI *(JECFA, 1988a, b).*

473. In considering the consequences of abuse and misuse, the following aspects need to be considered:

- The likelihood of violations or off-label use
- The residue levels occurring after such misuse or abuse
- The extent to which exposure to such residues will result in an exceedance of the ADI
- The likely frequency or period over which the ADI will be exceeded
- The acute consequences of exceeding the ADI
- The severity of the endpoint upon which the ADI is based
- The steepness of the dose-response curve for the endpoint upon which the ADI is based

474. Taking account of all of these factors, the data generated by the EU research in question do not provide any indication that it is not possible to conduct a risk assessment of the hormones used as growth promoters. Nor do they provide any indication that even such misuse or abuse as investigated gives rise to undue risk from the resultant residues, as intake would only very rarely exceed the ADI and then only on a rare occasion.

Alteration of gene expression by oestrogenic compounds

475. The study referred to (study 17), reported in *Leffers et al (2001),* showed that a number of oestogenic compounds affected the expression of several genes in the ERα positive breast cancer cell line, MCF7. The responsiveness of this cell line to oestrogens is well established. It was of interest that all of the changes reported by *Leffers et al (2001)* were blocked by the selective ERα antagonist ICI82.780. The relevance of effects observed in a cultured cell line to the situation *in vivo*, where kinetic and metabolic factors will influence the magnitude of the response is not known, nor is the significance of changes in gene expression to the toxicity of the hormones known. Many of the changes will reflect the proliferative response to an oestrogenic stimulus. However, in general toxicogenomic data, in the absence on any information on the functional consequences, is not considered a sound basis for use in risk assessment *(IPCS, 2003).*

IPCS (2003). Toxicogenomics and the Risk Assessment of Chemicals for the Protection of Human Health (http://www.who.int/entity/ipcs/methods/en/toxicogenomicssummaryreport.pdf)

Leffers H, Naesby M, Vendelbo B, Skakkebaek NE and Jorgensen M (2001). Oestrogenic potencies of Zeranol, oestradiol, diethylstilboestrol, Bisphenol-A and genistein: implications for exposure assessment of potential endocrine disrupters. Hum Reprod, 16:1037-1045.

Recent findings on the mutagenicity and genotoxicity and of oestradiol-17β

476. The recent reports (study 3 and study 8) on mutagenicity confirm that oestradiol can produce a genotoxic response in vitro in certain tests. Evidence was obtained that this was due, at least in part, to the formation of reactive oxygen species. Much of the work was undertaken with relatively high concentrations of metabolites added exogenously. For some of the genotoxic endpoints, oestradiol and the metabolites tested were negative. In one of the cited studies (*Chakravarti et al, 2001)* the effects of the 3,4-quinone metabolite were investigated in vivo. A relatively high dose was administered to mouse skin. Whilst mechanistic information of value can be obtained using a route other than the one of concern (i.e. oral for dietary residues), in this case there is concern that kinetic differences, particularly in the disposition of a quinone metabolite, make interpretation of the findings difficult, In addition, the mechanism for genotoxicity observed was not established, and the authors acknowledge that this could have been due to redox cycling. As indicated above, such a mechanism normally exhibits a threshold (see reply to question 19 above). It is known that compounds such as quinones can show marked route-dependent differences in their genotoxic effects. Indeed, several authorities, including the EC have accepted a threshold for the genotoxicity of some of these compounds in vivo following oral administration *(European Chemicals Bureau, 2006).* It was of interest that the mutations observed in vivo by *Chakravarti et al (2001)* in mouse skin involved adenine and not guanine. This is significant as it is the N7-guanine adducts that were "considered to play a crucial role in the initiation of oestrogen-dependent tumours" *(SCVPH, 2002).*

Chakravarti D, Mailander PC, Li KM, Higginbotham S, Zhang HL, Gross ML, Meza JL, Cavalieri EL and Rogan EG (2001). Evidence that a burst of DNA depurination in SENCAR mouse skin induces error-prone repair and forms mutations in the H-ras gene. Oncogene, 20:7945-7953

477. The genotoxicity and mutagenicity of oestradiol and, more particularly, its metabolites in vitro was already well established. No new evidence has been provided on the genotoxic potential of oestradiol in vivo. The study on the quinone metabolite on mouse skin does not further the risk assessment of the compound. No evidence was provided that oestradiol, or indeed any of its metabolites, is genotoxic in vivo following oral administration.

Recent findings on the biological effects of testosterone and progesterone

478. The SVCPH (2002) concluded in their report that on the basis of the most recently published papers "there is no evidence that progesterone or testosterone have genotoxic potential".

Recent findings on the biological effects of trenbolone and zeranol

Biotransformation

479. The metabolism of zeranol and trenbolone had been further investigated (study 4). These data do not appear to have been published in the peer reviewed literature to date.

480. The data on trenbolone show that the alpha enantiomer in liver slices from bovine is extensively conjugated and hence inactivated. There is some conversion of the alpha to the active beta isomer by human liver microsomes, but the kinetics of the reaction and the extent of conjugation have not been determined. No data were presented on levels of the alpha enantiomer in meat from treated cattle. However, these data do not affect the risk assessment of trenbolone acetate. This is because a) the toxicological studies were conducted in animals that would have been exposed to the

metabolites of concern, b) JECFA considered residues of both the alpha and the beta enantiomers in recommending MRLs for trenbolone acetate.

481. The study on zeranol suggested that some of the metabolites might undergo autooxidation. However, the extent of any such reaction in intact cells was not investigated, nor was the likely detoxication of the products formed. Perhaps more importantly, it is the toxicology of zeranol and its residues in meat that is at issue, and the evidence is such that it was possible to identify a threshold dose for all of the effects of concern.

Binding to sex hormone binding globulin

482. In this study (study 10), which does not appear to have been published in the peer reviewed literature, the interaction of growth promoting hormones with the binding of testosterone to plasma proteins was investigated. Some of the hormones, but not zeranol, were able to displace testosterone partially and only at concentrations very much higher then would ever be achieved from ingestion of meat from cattle treated even with high doses of the hormones for growth promotion. Hence, these findings have no significance for the risk assessment of the hormones. Although zeranol did not appear to bind to plasma proteins with high affinity, the ADI was established on the basis of the exogenous dose that had no effect. The fraction of protein binding should be the same for the ADI and the TMDI. Hence, the risk assessment of this hormone will not be affected by whether zeranol binds to plasma proteins or not.

Mutagenicity and genotoxicity

483. Study 4 reports recent observations on the genotoxicity and mutagenicity of zeranol and trenbolone. Both compounds were negative for tests of mutagenicity, i.e. induction of *lac*I mutations in *E coli* and induction of *hprt* mutations inV79 cells. Zeranol did not produce DNA adducts in rat hepatocytes whilst a low level of DNA adducts was observed with trenbolone. Both were very weakly positive in a micronucleus test, at high (potentially cytotoxic) concentrations. As indicated above (see my reply to question 21), micronuclei can arise via a non-genotoxic mechanism, particularly at concentrations that may have caused some toxicity. In addition, the 32P-post-labelling assay is not specific, and data cited above suggest that DNA adduction can arise by mechanisms other than direct interaction with DNA. These data are insufficient, given the number of well conducted studies in which the compounds were negative, to alter the conclusion that neither zeranol nor trenbolone acetate has genotoxic potential in vivo. Indeed, the *SVCPH (2002)* concluded that "both compounds exhibited only very weak effects" in those in vitro tests in which positive effects were observed.

Recent findings on the biological effects of MGA

Biotransformation

484. In study 4, unpublished preliminary findings on the in vitro metabolism of MGA were reported. This study provided some evidence for the formation of multiple metabolites of MGA by liver from human, rat and bovine. However, these findings do not affect the risk assessment of MGA because a) the toxicological studies were conducted in animals that would have been exposed to all of the metabolites of concern, b) JECFA assumed that all of the residues in meat from animals treated with MGA were as hormonally active as MGA when it proposed MRLs in 2002 *(JECFA, 2002b)*. It was subsequently shown that this was a conservative decision, as not all of the residues were as active as MGA itself *(JECFA, 2006c)*.

JECFA (2002b). Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper 41/14, Rome, Italy

JECFA (2006c). Residues of some veterinary drugs in animals and foods. FAO, Rome, Italy (in press)

MGA binding to sex hormone binding globulin

485. In study 10, preliminary and relatively poorly reported data on the interaction of MGA with the binding of testosterone to plasma proteins were presented. MGA, at concentrations very much higher than those that would arise from consumption of meat from animals treated with the hormone had some displacement activity against testosterone. The SCVPH (2002) commented on the absence of data on reproducibility in these studies and that in some experiments no concentration curves were developed. In conclusion, these findings do not alter the risk assessment of MGA.

Mutagenicity and genotoxicity of MGA

486. In study 4, MGA was negative in studies of the induction of *hprt* mutations in V79 cells, the induction of micronuclei in V79 cells and the induction of *lac*I mutations in *E coli*. Pure MGA had no effect on apoptosis, which could potentially confound interpretation of studies using V79 cells. Preliminary studies with rat liver slices, reported in an abstract but not yet published in the peer reviewed literature, suggested that MGA could produce unidentified adducts with DNA. As indicated above, there are mechanisms of adduct formation that do not involve direct interaction of the inducing compound with DNA. Overall, a report of putative covalent binding to DNA observed using 32P-post-labelling is not sufficient to over-ride the consistently negative results of MGA in a range of tests for mutagenicity. Hence, on the basis of the findings in study 5, there is no reasons to change the risk assessment or MGA.

Recent data on endocrine and developmental effects of the hormones

Experimental studies in rabbits

487. The EC commissioned a study on the effects of in utero exposure of rabbits to the three exogenous hormones, MGA, trenbolone acetate and zeranol (study 11). To date, only information on metabolism and disposition have been published *(Lange et al, 2002)*. Given the time that has elapsed since this paper was published (submitted September 2001), it is somewhat surprising the data from the remainder of the study have not been published.

488. The Lange et paper (2002) demonstrates transplacental transfer of the three hormones. This is not surprising given the physicochemical properties of the compounds (lipid solubility, non-polar, molecular size) *(Syme et al, 2004)*. In addition, endogenous hormones are known to cross the placenta. It is notable that in the study of Lange et al, fetal concentrations of the hormones and their metabolites were similar to or less than, sometimes much less than, those in corresponding maternal tissues, suggesting that there was no net accumulation of the compounds in fetal tissues. It is also noted that the number of animals studied was very small, a point commented on by the authors themselves.

*Lange IG, Daxenberger A, Meyer HH, Rajpert-De Meyts E, Skakkebaek NE and Veeramachaneni DN (2002). Quantitative assessment of foetal exposure to trenbolone acetate, zeranol and melengestrol acetate, following maternal dosing in rabbits. Xenobiotica, **32**:641-651*

Syme MR, Paxton JW and Keelan JA (2004). Drug transfer and metabolism by the human placenta. Clin Pharmacokinet, 43:487-514

489. The unpublished component of this study was an investigation of the potential health consequences of in utero exposure of rabbits to the three hormones. From the information provided, low dose exposure in utero caused modest changes in some parameters, but was not associated with either cancer or adverse effects on reproductive capacity. There were no changes in sperm number. It is not clear whether the changes observed were consistent and hence compound-related as a only a single dose was used for each compound. Nor is it apparent whether the magnitude of all of changes discussed reached statistical significance (often the changes were described as slight and no measure of variance is provided). The doses used in this study would have provided much higher levels of exposure than those predicted to arise from residues in meat. In the case of trenbolone acetate and zeranol exposure was via the subcutaneous route, thus bypassing presystemic metabolism in the intestine and/or the liver. In the case of MGA the oral dose was over 16,500 times the ADI. Hence, even if the effects observed were of toxicological significance the ADI would provide a more than adequate margin of protection.

490. Overall, this study cannot be said to confirm a risk to human health from consumption of meat from animals treated with these hormones.

In utero exposure and breast cancer: a study in opposite sexed twins

491. This study *(Kaijser et al, 2001*; study 13) showed an association between birth weight and risk of breast cancer. This is consistent with in utero exposure to oestrogens as a risk factor in breast cancer. However, it does not establish such a relationship. The authors note that "Although statistically significant (P=0.03), these estimates were based on small numbers in the extreme categories. However, when the data were categorized in more equally sized groups, the associations were similar and retained statistical significance, albeit with lower point estimates." There is no specific consideration of exposure to hormones present in meat from treated animals. The risk of such exposure, with respect to the hypothesis proposed by Kaisjer et al (2001) would depend on the mode of action and the dose-response relationship. A recent study *(de Assis et al, 2006)* suggests that higher birth weight per se can increase the risk of breast cancer. However, the significance of this study in experimental animals to humans has yet to be determined. Given that exposure to oestradiol from meat of treated animals would be extremely low, particularly relative to endogenous hormone levels, which increase during pregnancy, (e.g. see *Weiss, 2000*) the findings of the Kaisjer et al study provide no evidence for risk from exposure to oestradiol residues in meat from treated animals.

De Assis S, Khan G and Hilakivi-Clarke L (2006). High birth weight increases mammary tumorigenesis in rats. Int J Cancer (in press)

*Kaijser M, Lichtenstein P, Granath F, Erlandsson G, Cnattingius S and Ekbom A (2001). In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst, **93**:60-62*

*Weiss G (2000). Endocrinology of parturition. J Clin Endocrinol Metab, **85**:4421-4425*

492. Overall, this study cannot be said to confirm a risk to human health form consumption of meat from animals treated with these hormones.

Retrospective study on long-term effects in children of following suspected exposure to oestrogen-contaminated meat

493. This paper (*Chiumello et al, 2001*; study 12) reviews the increased incidence of gynocomastia in male children observed over a certain interval in a school in Milan, Italy. As oestradiol is known to cause gynocomastia, the authors speculated on the possible role of oestrogens, perhaps from meat of treated animals, as causative agents in these effects. However, this is entirely speculative, as no data were obtained to suggest that there had been any such exposure. Further, it was not possible to

establish whether oestrogens were involved at all, as there are a number of other risk factors for gynocomastia. Indeed, the SCVPH (2002) concluded that "As the reason for this incident remains unknown, the relevance of these data remains unclear".

Chiumello G, Guarneri MP, Russo G, Stroppa L and Sgaramella P (2001). Accidental gynocomastia in children. APMIS 109 (Suppl 103): S203-S209

494. Overall, this study cannot be said to confirm a risk to human health form consumption of meat from animals treated with these hormones.

Conclusion on the evidence from the studies initiated since 1997

495. There is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat from treated animals can be assessed. Whilst additional information has been obtained on a number of aspects of the hormones in question, this was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded on previous knowledge. The evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion.

496. My reply would have been the same at the time of adoption of the Directive by the EC in September, 2003.

Dr. Guttenplan

497. Yes, I see several important gaps. For instance:

498. It is not known if eating beef from hormone-treated animals substantially elevates the blood levels of estrogen/estrone in prepubescent children. This can probably be investigated.

499. It is not known if eating beef from hormone-treated animals substantially elevates the level of estrogenic activity in blood.

- Experiments on the identification, quantification, bioavailability and accumulation of lipoidal esters of estrogen in humans and experimental animals should be conducted.
- Epidemiological studies comparing adverse effects in matched populations of children eating beef from hormone-treated and untreated animals have not been reported.

[Please see the following references for the two questions above:
– paras. 58-94 and 125-129 of US First Submission, paras. 28-32 of US Rebuttal Submission
– paras. 116-124 of Canada First Submission, paras. 74, 130-135 of Canada Rebuttal Submission (Exhibit CDA-23)
– paras. 108, 147, 162-169 of EC Replies to Panel Questions, paras. 143-174 of EC Rebuttal Submission (US case), and paras. 148-166 of EC Rebuttal Submission (Canada case)
– Exhibit CDA-32 provides a detailed table outlining the chronology of JECFA's assessment of these hormones and the resulting documentation]

ATTACHMENT 1

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ATTACHMENT 2

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WORLD TRADE ORGANIZATION

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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex E to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex B: Add.2
- Annex C: Add.3
- Annex D: Add.4
- Annex F: Add.6
- Annex G: Add.7

ANNEX E

REPLIES OF THE CODEX ALIMENTARIUS COMMISSION, THE JOINT FAO/WHO JECFA SECRETARIAT AND THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

ANNEX E-1

REPLIES OF THE CODEX ALIMENTARIUS COMMISSION TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

1. Please briefly describe the procedure for the elaboration and adoption of an international standard by Codex. What is the decision-making process for the adoption of an international standard?

The procedure for the elaboration and adoption of Codex standards and related texts are published in the *Procedural Manual of the Codex Alimentarius Commission* (see Annex 1). The Procedure for the Elaboration of Codex Standards was comprehensively revised in 1993 to provide a uniform elaboration procedure for all Codex standards and related texts, including maximum residue limits (consisting of 8 Steps under the normal procedure and 5 Steps under the accelerated procedure). The revised uniform elaboration procedure superseded the separate procedure for the elaboration of Codex Maximum Residue Limits (MRLs) for Veterinary Drugs.[1] The Procedure was further revised in 2004 to introduce the strategic planning process and the critical review of new work proposals at Step 8.

In essence the *8-step procedure* followed in the development and approval of the standard involves:

Prior to Step 1: The *submission of a proposal* for a new standard or related text by a national government or a subsidiary body of the Commission. This is usually accompanied by a project document that indicates the purpose, scope and proposed timeline time frame for the new work. The project document is reviewed by the Executive Committee, which forward its opinion to the Commission (this process is called "critical review").

In the case of MRLs for veterinary drugs, submission of project documents is not required; instead, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) prepares a priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA, which is submitted to the Commission for approval.

Step 1 — a *decision by the Commission that a standard be developed* as proposed. "Criteria for the Establishment of Work Priorities" exist to assist the Commission in its decision-making and in selecting the subsidiary body to be responsible for steering the standard through its development. If necessary, a new subsidiary body – usually a specialized task force - may be created. In the case of matters related to the residues of veterinary drugs, CCRVDF always undertakes the standards development work assigned by the Commission in accordance with its terms of reference (Annex 2);

Step 2 — the preparation of a proposed draft standard;

[1] Elaborated by the CCRVDF and adopted by the 18th Session of the Codex Alimentarius Commission (1989) (ALINORM 89/40 para. 215). The 8-step procedure, involved: Steps 1, 2 and 3: the distribution of the draft recommendations for MRLs for veterinary drugs, based on JECFA evaluations and request comments from Government and interested organisation; Step 4: examination by the CCRVDF in the light of the comments. The CCRVDF, when formulating its recommendations for proposed draft MRLs, takes all appropriate matters into consideration including the need for urgency, the government comments at Step 3 and the likelihood of new evidence becoming available in the immediate future and, on the basis of such considerations, indicates to the Commission those proposed draft MRLs which, in its view, need to be passed through the full Procedure and those for which there might be an omission of Step 6 and 7; Steps 5-8: as for the Procedure for the Elaboration of world-wide standards.

Step 3 the circulation of the proposed draft standard for governments' and interested organizations' comments; in the case of MRLs for veterinary drugs, the recommendations of JECFA are circulated for comments at this Step;

Step 4 the discussion at Committee level;

Step 5 the submission of the proposed draft standard to the Commission for adoption as draft standard ("preliminary adoption");

Step 6 the circulation of the draft standard for governments' and interested organizations' comments;

Step 7 the discussion at Committee level;

Step 8 the submission of the draft standard to the Commission for adoption as Codex standard.

More details of the Elaboration Procedure are given in Annex 1.

A Committee may decide to submit a text to the Commission for adoption at Step 5 and 8, with the omission of Steps 6 and 7. The Commission may also approve the use of an *accelerated* procedure for the elaboration of these standards, using a 5-step elaboration process.

The Commission may also decide to return a proposed draft or a draft standard from Step 5 or 8 to a previous step when it considers that more discussion is necessary at the Committee level.

The procedure for revision of Codex standards and related texts follows that used for the elaboration of standards. The Commission and its subsidiary bodies are committed to the revision of Codex standards and related texts as necessary to ensure they are consistent with and reflect current scientific knowledge. Each member of the Commission is responsible for identifying and presenting to the appropriate committee any new scientific and other relevant information that may warrant revision of existing Codex standards or related texts.

The *Procedure for the Elaboration of Codex Standards and Related Texts* allows for full discussion and exchange of views on the issue under consideration, in order to ensure the transparency of the process and, if necessary, arrive at compromises that would facilitate consensus. Written comments from governments and observers are solicited at Steps 3, 5, 6 and 8; furthermore, governments and observers can present their positions directly in a committee meeting and exchange views with other delegations at Steps 4 and 7.

The Commission attaches a great importance of achieving consensus at all stages of the elaboration of standards and that draft standards should, as a matter of principle, be submitted to the Commission for adoption only where consensus has been achieved at the technical level. For this purpose, the Commission at its 26th Session (2003) adopted "Measures to Facilitate Consensus" for inclusion in the Procedural Manual (see Annex 3).

2. Please briefly explain the differences between Codex standards, codes of practice, guidelines, principles and other recommendations.

The texts developed by the Codex Alimentarius Commission may be divided in two main groups: i) texts intended for use by Governments and are published in the Codex Alimentarius (these include Codex standards, codes of practice, guidelines, principles and other recommendations); and ii) texts

intended to guide the work of the Commission and its subsidiary bodies and are included in the Procedural Manual (these include the Statutes and Rules of Procedure of the Commission, other procedures, guidelines, principles and other recommendations.)

Codex standards usually relate to product characteristics and may deal with all government-regulated characteristics appropriate to the commodity, or only one characteristic. Maximum residue limits (MRLs) for residues of veterinary drugs in foods are examples of standards dealing with only one characteristic (i.e. numerically expressed limits of a chemical substance in a given food (animal tissue or milk)). There are *Codex general standards* for food additives and contaminants and toxins in foods that contain both general and commodity-specific provisions. The Codex General Standard for the Labelling of Prepackaged Foods covers all foods in this category. Codex commodity standards, on the other hand, include provisions on the product definition, essential quality factors, labelling and health-related aspects for a given product or a group of products. Because standards relate to product characteristics, they can be applied wherever the products are traded. *Codex methods of analysis and sampling*, including those for contaminants and residues of pesticides and veterinary drugs in foods, are also considered Codex standards.

Codex codes of practice (including codes of hygienic practice) define the production, processing, manufacturing, transport and storage practices for individual foods or groups of foods that are considered essential to ensure the safety and suitability of food for consumption. For food hygiene, the basic text is the Codex General Principles of Food Hygiene, which recommends the use of the Hazard Analysis and Critical Control Point (HACCP) food safety management system. The Codex Code of Practice on the Control of the Use of Veterinary Drugs provides general guidance in relation to the use of veterinary drugs in food production.

Codex guidelines fall into two categories: i) principles that set out policy in certain key areas; and ii) guidelines for the interpretation of these principles or for the interpretation and/or application of the provisions of the Codex general standards.

Codex guidelines include those for food labelling, especially the regulation of claims made on the label. This group includes guidelines for nutrition and health claims; conditions for production, marketing and labelling of organic foods; and foods claimed to be "halal". There are several guidelines that interpret the provisions of the Codex Principles for Food Import and Export Inspection and Certification, and guidelines on the conduct of safety assessments of foods from DNA-modified plants and micro-organisms.

The status of Codex standards and related texts within the Codex system and in the international framework has changed several times since the Commission was established in 1962.

These changes can be identified in four periods: until 1981; from 1981 to 1995; from 1995 to 2006; and since 2006 when Codex Acceptance Procedures were formally abolished.

Until 1981 – The elaboration of a worldwide standard consisted of 11 Steps until the Steps beyond Step 8 were eliminated in the 5th Edition of the Procedural Manual. The eliminated Steps were: Step 9 (the "recommended standard" is sent to FAO/WHO members for acceptance, and the latter notify their acceptance); Step 10 (the Secretariat periodically publishes notifications received on the recommended standard); Step 11 (the "recommended standard" is published as a "Codex standard" when the Commission determines that it is appropriate to do so in the light of notifications received).

From 1981 to 1995 – Codex Standards and Related Texts had habitually been classified on the basis of whether or not texts are intended to be subject to the Acceptance Procedures laid down in paragraphs 4, 5 and 6 of the General Principles of the Codex Alimentarius (see Procedural Manuals prior to the 15th Edition; e.g. Annex 4). Those adopted texts subjected to the Acceptance Procedures

were termed "mandatory" and the other texts "advisory". The term "mandatory" did not mean that members were under obligations to accept Codex standards as were. Members could choose among three different forms of acceptance: "Full Acceptance"; "Acceptance with specified deviations"; and "Free distribution[2]", in accordance with their own legal and administrative procedures. The situation was different regarding the acceptance of Codex Maximum Limits for Residues of Pesticides and Veterinary Drugs in Food. In this case, the General Principles of the Codex Alimentarius only provided the possibility of Full Acceptance or Free Distribution (see section 6, Annex 4).

Prior to the establishment of the WTO in 1995 and the entry in force of the WTO Agreements on the Application of Sanitary and Phytosanitary (SPS) Measures and on Technical Barrier to Trade (TBT), the status of Codex standards was defined only within the Codex system; in particular they had no direct binding effect on member countries per se. Countries were undertaking specific obligations only when they declared acceptance according to one of the modalities indicated in section 4A, 5A and 6A of the General Principles of the Codex Alimentarius (Annex 4). In particular, a country had the obligation to accept a product for distribution on its territory only when it has declared acceptance.

The notifications of acceptance received in the Codex Secretariat became increasingly rare by the end of 1980s, because many countries ceased to implement a national procedure for the acceptance of standards. The Progress Report on Acceptances was a standing item in the agenda of the Commission since its early years but was discontinued after 1993, and was replaced by a discussion on the usefulness of acceptances in the light of the WTO Agreements. Acceptances were published in 1989 for standards and in 1983 for pesticide residues for the last time. Notifications became very rare in the 1990s.

From 1995 to 2006 - Codex standards and related texts started to enjoy a new status in the framework of WTO Agreements. In regard to the differences between standards, guidelines and other recommendations, It is worth noting the clarification provided by the WTO SPS Committee in March 1998 in response to the query sent from Codex: the SPS Committee responded that the provisions of the SPS Agreement did not differentiate between the three terms "standards", "guidelines" or "recommendations" (see Annex 5).

Meanwhile, the 22nd Session of the Codex Alimentarius Commission (1997) agreed that the use of the terms "mandatory" and "advisory" was confusing and not consistent with the provisions of the SPS and TBT Agreements, and stated that they should no longer be used.[3] Once standards and related texts have been adopted by the Codex Alimentarius Commission, they are recognized as a reference under the SPS Agreement in matters of food safety and under TBT for other technical matters relevant to food regulation.

After 2006 (abolition of Codex Acceptance Procedures)

The 28th Session of the Codex Alimentarius Commission (2005) agreed to abolish the acceptance procedures and amend relevant section of the Procedural Manual accordingly.[4] As stated above, the Codex acceptance procedure covered only Codex Standards (Commodity or General) and Maximum Residue Limits, and did not cover other texts adopted by the Commission, such as codes of practice and other recommendations. As a consequence of abolishing acceptance procedure, the dichotomy between "standards and MRLs" and "other texts" within the Codex Alimentarius was removed, resulting in a uniform status of all Codex standards and related texts.

[2] "Free Distribution" was introduced as a new category of acceptance in 1989 by the 18th Session of the Commission.

[3] ALINORM 97/37, para. 171.

[4] ALINORM 05/28/41, para. 36.

3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

The Codex Alimentarius Commission initiated work to incorporate risk assessment principles into Codex decision-making and procedures on the basis of the Joint FAO/WHO Conference on Food Standards, Chemicals in Food and Food Trade, held in Rome in 1991. The Commission, at its 19th and 20th Session agreed on the incorporation of risk assessment principles in its procedure. To assist the Commission, FAO and WHO convened a joint FAO/WHO expert consultation on the application of risk analysis to food standards issues in 1995.

The *Statements of principles relating to the role of food safety risk assessment*[5], adopted by the 22nd Session of the Codex Alimentarius Commission (1997), state that:

> *1. Health and safety aspects of Codex decisions and recommendations should be based on a risk assessment, as appropriate to the circumstances.*
>
> *2. Food safety risk assessment should be soundly based on science, should incorporate the four steps of the risk assessment process, and should be documented in a transparent manner.*
>
> *3. There should be a functional separation of risk assessment and risk management, while recognizing that some interactions are essential for a pragmatic approach.*
>
> *4. Risk assessment should use available quantitative information to the greatest extent possible and risk characterizations should be presented in a readily understandable and useful form.*

The 22nd Session of the Commission also adopted an Action Plan for Codex-wide Development and Application of Risk Analysis Principles and Guidelines. In accordance with the Plan and on the basis of the preparatory work by the Codex Committee on General Principles, the 26th Session of the Codex Alimentarius Commission (2003) adopted the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* for inclusion in the Procedural Manual[6] (see Annex 6). The objective of the Principles is to provide guidance to Codex subsidiary bodies and FAO/WHO expert bodies and consultations, so that food safety and health aspects of Codex standards and related texts are based on risk analysis. The Principles clearly define the responsibilities of the Commission and its subsidiary bodies for risk management decision and of the joint FAO/WHO expert bodies and consultation for risk assessment.

Following the adoption of the Working Principles, the Commission requested that relevant Codex Committees develop or complete specific guidelines on risk analysis in their respective areas for inclusion in the Procedural Manual. The Commission noted that these texts would be submitted to the Committee on General Principles in order to ensure coordination of work and consistency with the overarching Working Principles.[7] At the same time, the Committee on General Principles pursued elaboration of risk analysis guidance for use by governments (this work is still ongoing).

Within the framework of the above request by the Commission, the 16th Session of the CCRVDF (2006) completed work on: "Risk Analysis Principles applied by the Codex Committee on Residues

[5] Procedural Manual of the Codex Alimentarius Commission (15th Edition).
[6] ALINORM 03/41, para. 146 and Appendix IV.
[7] ALINORM 03/41, para. 147.

of Veterinary Drugs in Foods" and "Risk Assessment Policy for the Setting of MRLs in Food" and forwarded these to the Codex Alimentarius Commission.[8] The two documents will be considered by the 30th Session of the Codex Alimentarius Commission in 2007 (after review by the Codex Committee on General Principles) for adoption and inclusion in the Procedural Manual.

The Principles define the responsibilities of the various parties involved: the responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission (CAC) and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRDVF), while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

The Risk Assessment Policy applies to the work of JECFA in the context of Codex and in particular as it relates to advice requests from CCRVDF.

4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

There is no adopted Codex standard or related text on the risk assessment of residues on veterinary drugs that provides guidance to governments. However, at the request of 23rd session of the Commission, the CCRVDF in 2000 started develop texts on risk analysis principles in the work of the Committee. The 16th Session of the Committee completed work on two texts: Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and Risk Assessment Policy for the Setting of MRLs in Food, for inclusion in the Procedural Manual (see the answer to Question 3, above). The documents may be adopted by the Commission in 2007. Annex 7 describes relevant discussion in CCRVDF to strengthen science -based approach to risk analysis into its work.

As other internal documents on risk analysis, Codex has already adopted Risk Analysis Principles Applied by the Codex Committee on Food Additives and Contaminants and CCFAC Policy for Exposure Assessment of Contaminants and Toxins in Foods and Food Groups; the Commission will possibly adopt Risk Analysis Principles Applied by the Codex Committee on Pesticides Residues, finalized by the 38th Session of the CCPR (2006) in 2007.

As the adopted texts on risk analysis providing guidance to governments, Codex has: Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999); and Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (CAC/GL 44-2003) and two accompanying guidelines for food safety assessment of foods derived from recombinant-DNA plants and microorganisms (CAC/GL 45-2003; CAC/GL 46-2003).

In addition, the Codex Committee on Food Hygiene (CCFH) is currently developing Principles and Guidelines for the Conduct of Microbiological Risk Management (at Step 6) and the *ad hoc* Codex Intergovernmental Task Force on Biotechnology is working on Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals.

5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) as defined by Codex and explain how they differ.

[8] ALINORM 06/29/31 para. 111 and Appendices VIII and IX.

Definitions of Risk Analysis Terms related to Food Safety were adopted by the 22nd Session of the Codex Alimentarius Commission[9] (1997) and were included in the Procedural Manual (see Annex 8). The definitions of "Risk Management" and "Risk Communication" were revised by the 23rd Session of the Codex Alimentarius Commission (1999) [10] in the light of the reports of the Joint FAO/WHO Experts Consultations on Risk Management and Food Safety and on Risk Communication in Relation to Food Standards and Safety Matters. The *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* describe the three components of risk analysis in more detail (see Annex 6).

The Procedural Manual of the Codex Alimentarius Commission provides the following definitions (*in italics*):

Risk Assessment: *A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization* [11]

Risk Management: *The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.*[11]

Risk Communication: *The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.*[11]

6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

The Procedural Manual of the Codex Alimentarius Commission provides the following definitions (*in italics*):

Hazard identification. *The identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in food.*[11]

Hazard characterization. *The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.*[11]

Exposure assessment. *The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.*[11]

Risk characterization. *The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.*[11]

[9] ALINORM 97/37, para. 31 and Appendix II.
[10] ALINORM 99/37, para. 70 and Appendix IV.
[11] Procedural Manual of the Codex Alimentarius Commission (15th Edition).

9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

A definition for *Codex Maximum Limits of Residues of Veterinary Drugs* (MRLVD) is contained in the Procedural Manual of the Codex Alimentarius Commission (see below). A definition for *Acceptable Daily Intake* (ADI) is included in the "Glossary of Terms and Definition" (CAC/MISC 5 1993) (see below), which has been elaborated by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) with a view of providing information and guidance to the Committee, and it is intended for internal Codex use only.[12]

> ***Codex Maximum Residue Limit for Veterinary Drugs (MRLVD)*** *is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.*
>
> *It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.*
>
> *When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.*[11]
>
> ***Acceptable Daily Intake (ADI):*** *An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg) (Note - definition previously established and adopted by the JECFA, which has been modified by the Codex Committee on Veterinary Drugs in Foods).*[13]

12. In para. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

The Terms of Reference of the CCRVDF also include the development of codes of practice (Annex 2). The development of a Code of Practice might therefore be considered by the Committee as a possible option to manage risks related to residues of veterinary drugs.

The CCRVDF, at its 16th Session, agreed to the preparation of a discussion paper to identify risk management issues to be addressed by the Committee and re-established the Working Group on Substance with no ADI/MRL in order to, *inter alia*, consider management option for compound to be evaluated by JECFA where a management decision is pending.[14]

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[12] Please note that Codex does not adopt ADI. JECFA MRLs and ADI are separate outputs of the risk assessment process and only JECFA recommendations for MRLs are considered by the Codex process.

[13] Glossary of Terms and Definition" (CAC/MISC 5-1993).

[14] ALINORM 06/29/31 paras 113 and 134.

15. Please provide the definition of the term Good Veterinary Practice (GVP). Are there any relevant Codex standards, guidelines, or recommendations relating to GVP?

There is no a Codex definition of the term Good Veterinary Practice (GVP). Codex has developed a definition of the term ***Good Practice in the Use of Veterinary Drug (GPVD)***, which is contained in the Procedural Manual of the Codex Alimentarius Commission (see below).

> ***Good Practice in the Use of Veterinary Drugs (GPVD)*** *is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.*[12]

Relevant texts related to GPVD include:

– The recommended international "*Code of Practice for the Control of the Use of Veterinary Drugs*" (CAC/RCP 38-1993) sets out guidelines on the prescription, application, distribution and control of drugs used for treating animals, preserving animal health or improving animal production (see Annex 9);

– Codex *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* (CAC/GL 16-1993) (see Annex 10). Please Note that CCRVDF is currently working on a revision of the Guidelines (the 16th Session of CCRVDF has forwarded a proposed draft of the Guidelines to the 29th Session of the Codex Alimentarius Commission for preliminary adoption at Step 5).[15]

16. Please provide an update on the status of international standards with respect to the six hormones at issue. What are the remaining procedures before the adoption of a standard on melengestrol acetate (MGA)? What is the timeframe for their completion?

Oestradiol-17β – MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since the 12th CCRVDF (2000);

Progesterone – MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since the 12th CCRVDF (2000);

Testosterone – MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since the 12th CCRVDF (2000);

Trenbolone acetate - MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since 7th CCRVDF (1992);

Zeranol - MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since 7th CCRVDF (1992);

Melengestrol acetate – Currently under consideration by CCRVDF. Annex 11 provides a chronological history of the CCRVDF consideration of MGA.

18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

[15] ALINORM 06/29/31, para. 86 and Appendix VII.

According to the *Procedure of the Elaboration of Codex Standard and Related Texts*, it will be for the Commission itself to keep under review the revision of "Codex standards" (see Annex 1, para. 8) and instruct Codex subsidiary bodies to undertake this work. Proposals for new work, including the revision of Codex Standards, are also submitted to the Commission by a Codex subsidiary body or a Codex Member.

In the case of estradiol-17 beta, progesterone and testosterone, they were re-evaluated by the 52nd JECFA (1999) at the initiative of the JECFA Secretariat. The 12th CCRVDF (2000), in recognising that it had not requested the re-evaluation of the three substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, decided to not consider the new recommendation of the 52nd JECFA.[16]

In the case of MGA, the 58th JECFA has re-evaluated MGA at the request of the 14th CCRVDF on the basis of new information and additional data to be submitted.[17] During the discussion on MGA at the 16th CCRVDF, there was no request for a further re-evaluation of MGA.[18]

[16] ALINORM 01/31, para. 84.
[17] ALINORM 99/213/31, para 113 and Appendix VII.
[18] ALINORM 06/29/31, para. 69.

List of Annexes

Other References:

Reports of the past sessions (1st to 16th) of the Codex Committee on Residues of Veterinary Drugs in Foods

WHO 1995. *Application of Risk Analysis to Food Standards Issues*. Report of the Joint FAO/WHO Expert Consultation. Geneva, Switzerland, 13-17 March 1995. WHO/FNU/FOS/95.3

FAO. 1997. *Risk management and food safety*. Report of a Joint FAO/WHO Consultation. Food and Nutrition Paper 65. Rome.

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FAO/WHO. 2006 (in preparation). *The use of microbiological risk assessment outputs to develop practical risk management strategies*. Report of a joint FAO/WHO meeting, Kiel, Germany, 3-7 April, 2006.

ANNEX 1

PROCEDURES FOR THE ELABORATION OF CODEX STANDARDS AND RELATED TEXTS[1]

Note: These procedures apply to the elaboration of Codex standards and related texts (e.g, codes of practice, guidelines) adopted by the Codex Alimentarius Commission as recommendations for governments.

INTRODUCTION

The full procedure for the elaboration of Codex standards is as follows.

1. The Commission shall implement a unified approach in the area of standards development by taking its decisions, based on a strategic planning process ("standards management") (See Part 1 of this document).

2. An on-going critical review shall ensure that proposals for new work and draft standards submitted to the Commission for adoption continue to meet the strategic priorities of the Commission and can be developed within a reasonable period of time, taking into account the requirements and availability of scientific expert advice (See Part 2 of this document).

3. The Commission decides, taking into account the outcome of the on-going critical review conducted by the Executive Committee, that a standard should be elaborated and also which subsidiary body or other body should undertake the work. Decisions to elaborate standards may also be taken by subsidiary bodies of the Commission in accordance with the above-mentioned outcome subject to subsequent approval by the Commission at the earliest possible opportunity. The Secretariat arranges for the preparation of a "proposed draft standard" which is circulated to governments for comments and is then considered in the light of these by the subsidiary body concerned which may present the text to the Commission as a "draft standard". If the Commission adopts the "draft standard" it is sent to governments for further comments and in the light of these and after further consideration by the subsidiary body concerned, the Commission reconsiders the draft and may adopt it as a "Codex standard". The procedure is described in Part 3 of this document.

4. The Commission or any subsidiary body, subject to the confirmation of the Commission may decide that the urgency of elaborating a Codex standard is such that an accelerated elaboration procedure should be followed. While taking this decision, all appropriate matters shall be taken into consideration, including the likelihood of new scientific information becoming available in the immediate future. The accelerated elaboration procedure is described in Part 4 of this document.

5. The Commission or the subsidiary body or other body concerned may decide that the draft be returned for further work at any appropriate previous Step in the Procedure. The Commission may also decide that the draft be held at Step 8.

6. The Commission may authorise, on the basis of two-thirds majority of votes cast, the omission of Steps 6 and 7, where such an omission is recommended by the Codex Committee entrusted with the elaboration of the draft. Recommendations to omit steps shall be notified to Members and interested international organizations as soon as possible after the session of the Codex Committee concerned. When formulating recommendations to omit Steps 6 and 7, Codex Committees shall take all appropriate matters into consideration, including the need for urgency, and the likelihood of new scientific information becoming available in the immediate future.

[1] Procedural Manual of the Codex Alimentarius Commission (15th Edition).

7. The Commission may at any stage in the elaboration of a standard entrust any of the remaining Steps to a Codex Committee or other body different from that to which it was previously entrusted.

8. It will be for the Commission itself to keep under review the revision of "Codex standards". The procedure for revision should, *mutatis mutandis*, be that laid down for the elaboration of Codex standards, except that the Commission may decide to omit any other step or steps of that Procedure where, in its opinion, an amendment proposed by a Codex Committee is either of an editorial nature or of a substantive nature but consequential to provisions in similar standards adopted by the Commission at Step 8.

9. Codex standards and related texts are published and are sent to governments as well as to international organizations to which competence in the matter has been transferred by their Member States (see Part 5 of this document).

PART 1. STRATEGIC PLANNING PROCESS

1. Taking into account the "*Criteria for the Establishment of Work Priorities*", the strategic plan shall state broad priorities against which individual proposals for standards (and revision of standards) can be evaluated during the critical review process.

2. The strategic plan shall cover a six-year period and shall be renewed every two years on a rolling basis.

PART 2. CRITICAL REVIEW

Proposals to Undertake New Work or to Revise a Standard

1. Prior to approval for development, each proposal for new work or revision of a standard, shall be accompanied by a project document, prepared by the Committee or Member proposing new work or revision of a standard, detailing:

- the purposes and the scope of the standard;
- its relevance and timeliness;
- the main aspects to be covered;
- an assessment against the *Criteria for the establishment of work priorities;*
- relevance to the Codex strategic objectives;
- information on the relation between the proposal and other existing Codex documents;
- identification of any requirement for and availability of expert scientific advice;
- identification of any need for technical input to the standard from external bodies so that this can be planned for;
- the proposed time-line for completion the new work, including the start date, the

proposed date for adoption at Step 5, and the proposed date for adoption by the Commission; the time frame for developing a standard should not normally exceed five years.

2. The decision to undertake new work or to revise standards shall be taken by the Commission taking into account a critical review conducted by the Executive Committee.

3. The critical review includes:

- examination of proposals for development/revision of standards, taking into account the "*Criteria for the Establishment of Work Priorities*", the strategic plan of the Commission and the required supporting work of independent risk assessment;
- identifying the standard setting needs of developing countries;
- advice on establishment and dissolution of committees and task forces, including *ad hoc* cross-committee task forces (in areas where work falls within several committee mandates); and
- preliminary assessment of the need for expert scientific advice and the availability of such advice from FAO, WHO or other relevant expert bodies, and the prioritisation of that advice.

4. The decision to undertake new work or revision of individual maximum residue limits for pesticides or veterinary drugs, or the maintenance of the General Standard on Food Additives[2], the General Standard on Contaminants and Toxins in Foods[3], the Food Categorisation System and the International Numbering System, shall follow the procedures established by the Committees concerned and endorsed by the Commission.

Monitoring Progress of Standards Development

5. The Executive Committee shall review the status of development of draft standards against the time frame agreed by the Commission and shall report its findings to the Commission.

6. The Executive Committee may propose an extension of the time frame; cancellation of work; or propose that the work be undertaken by a Committee other than the one to which it was originally entrusted, including the establishment of a limited number of *ad hoc* subsidiary bodies, if appropriate.

7. The critical review process shall ensure that progress in the development of standards is consistent with the envisaged time frame, that draft standards submitted to the Commission for adoption have been fully considered at Committee level.

8. Monitoring shall take place against the time line deemed necessary and revisions in the coverage of the standard shall need to be specifically endorsed by the Commission.

This shall therefore include:

- monitoring of progress in developing standards and advising what corrective action should be taken;

[2] including related methods of analysis and sampling plans
[3] including related methods of analysis and sampling plans

- examining proposed standards from Codex committees, before they are submitted to the Commission for adoption:

  – for consistency with the mandate of Codex, the decisions of the Commission, and existing Codex texts,

  – to ensure that the requirements of the endorsement procedure have been fulfilled, where appropriate,

  – for format and presentation, and

  – for linguistic consistency.

PART 3. UNIFORM PROCEDURE FOR THE ELABORATION OF CODEX STANDARDS AND RELATED TEXTS

Steps 1, 2 and 3

(1) The Commission decides, taking into account the outcome of the critical review conducted by the Executive Committee, to elaborate a World-wide Codex Standard and also decides which subsidiary body or other body should undertake the work. A decision to elaborate a World-wide Codex Standard may also be taken by subsidiary bodies of the Commission in accordance with the above mentioned outcome, subject to subsequent approval by the Commission at the earliest possible opportunity. In the case of Codex Regional Standards, the Commission shall base its decision on the proposal of the majority of Members belonging to a given region or group of countries submitted at a session of the Codex Alimentarius Commission.

(2) The Secretariat arranges for the preparation of a proposed draft standard. In the case of Maximum Limits for Residues of Pesticides or Veterinary Drugs, the Secretariat distributes the recommendations for maximum limits, when available from the Joint Meetings of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR), or the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Any other relevant information regarding risk assessment work conducted by FAO and WHO should also be made available. In the cases of milk and milk products or individual standards for cheeses, the Secretariat distributes the recommendations of the International Dairy Federation (IDF).

(3) The proposed draft standard is sent to Members of the Commission and interested international organizations for comment on all aspects including possible implications of the proposed draft standard for their economic interests.

Step 4

The comments received are sent by the Secretariat to the subsidiary body or other body concerned which has the power to consider such comments and to amend the proposed draft standard.

Step 5

The proposed draft standard is submitted through the Secretariat to the Executive Committee for

critical review and to the Commission with a view to its adoption as a draft standard[4]. In taking any decision at this step, the Commission will give due consideration to the outcome of the critical review and to any comments that may be submitted by any of its Members regarding the implications which the proposed draft standard or any provisions thereof may have for their economic interests. In the case of Regional Standards, all Members of the Commission may present their comments, take part in the debate and propose amendments, but only the majority of the Members of the region or group of countries concerned attending the session can decide to amend or adopt the draft. In taking any decisions at this step, the Members of the region or group of countries concerned will give due consideration to any comments that may be submitted by any of the Members of the Commission regarding the implications which the proposed draft standard or any provisions thereof may have for their economic interests.

Step 6

The draft standard is sent by the Secretariat to all Members and interested international organizations for comment on all aspects, including possible implications of the draft standard for their economic interests.

Step 7

The comments received are sent by the Secretariat to the subsidiary body or other body concerned, which has the power to consider such comments and amend the draft standard.

Step 8

The draft standard is submitted through the Secretariat to the Executive Committee for critical review and to the Commission, together with any written proposals received from Members and interested international organizations for amendments at Step 8, with a view to its adoption as a Codex standard. In the case of Regional standards, all Members and interested international organizations may present their comments, take part in the debate and propose amendments but only the majority of Members of the region or group of countries concerned attending the session can decide to amend and adopt the draft.

PART 4. UNIFORM ACCELERATED PROCEDURE FOR THE ELABORATION OF CODEX STANDARDS AND RELATED TEXTS

Steps 1, 2 and 3

(1) The Commission, on the basis of a two-thirds majority of votes cast, taking into account the outcome of the critical review conducted by the Executive Committee, shall identify those standards which shall be the subject of an accelerated elaboration process.[5] The identification of such standards may also be made by subsidiary bodies of the Commission, on the basis of a two-thirds majority of votes cast, subject to confirmation at the earliest opportunity by the Commission.

[4] Without prejudice to the outcome of the critical review conducted by the Executive Committee and/or any decision that may be taken by the Commission at Step 5, the proposed draft standard may be sent by the Secretariat for government comments prior to its consideration at Step 5, when, in the opinion of the subsidiary body or other body concerned, the time between the relevant session of the Commission and the subsequent session of the subsidiary body or other body concerned requires such action in order to advance the work

[5] Relevant considerations could include, but need not be limited to, matters concerning new scientific information; new technology(ies); urgent problems related to trade or public health; or the revision or up-dating of existing standards.

(2) The Secretariat arranges for the preparation of a proposed draft standard. In the case of Maximum Limits for Residues of Pesticides or Veterinary Drugs, the Secretariat distributes the recommendations for maximum limits, when available from the Joint Meetings of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR), or the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Any other relevant information regarding risk assessment work conducted by FAO and WHO should also be made available. In the cases of milk and milk products or individual standards for cheeses, the Secretariat distributes the recommendations of the International Dairy Federation (IDF).

(3) The proposed draft standard is sent to Members of the Commission and interested international organizations for comment on all aspects including possible implications of the proposed draft standard for their economic interests. When standards are subject to an accelerated procedure, this fact shall be notified to the Members of the Commission and the interested international organizations.

Step 4

The comments received are sent by the Secretariat to the subsidiary body or other body concerned which has the power to consider such comments and to amend the proposed draft standard.

Step 5

In the case of standards identified as being subject to an accelerated elaboration procedure, the draft standard is submitted through the Secretariat to the Executive Committee for critical review and to the Commission**,** together with any written proposals received from Members and interested international organizations for amendments, with a view to its adoption as a Codex standard. In taking any decision at this step, the Commission will give due consideration to any comments that may be submitted by any of its Members regarding the implications which the proposed draft standard or any provisions thereof may have for their economic interests.

PART 5. SUBSEQUENT PROCEDURE CONCERNING PUBLICATION OF CODEX STANDARDS

The Codex standard is published and issued to all Member States and Associate Members of FAO and/or WHO and to the international organizations concerned.

The above mentioned publications will constitute the *Codex Alimentarius*.

SUBSEQUENT PROCEDURE CONCERNING PUBLICATION AND POSSIBLE EXTENSION OF TERRITORIAL APPLICATION OF THE STANDARD

The Codex Regional Standard is published and issued to all Member States and Associate Members of FAO and/or WHO and to the international organizations concerned.

It is open to the Commission to consider at any time the possible extension of the territorial application of a Codex Regional Standard or its conversion into a World-wide Codex Standard.

GUIDE TO THE CONSIDERATION OF STANDARDS AT STEP 8 OF THE PROCEDURE FOR THE ELABORATION OF CODEX STANDARDS INCLUDING CONSIDERATION OF ANY STATEMENTS RELATING TO ECONOMIC IMPACT

1. In order:

   (a) to ensure that the work of the Codex committee concerned is not made less valuable by the passage of an insufficiently considered amendment in the Commission;

   (b) at the same time to provide scope for significant amendments to be raised and considered in the Commission;

   (c) to prevent, as far as practicable, lengthy discussion in the Commission on points that have been thoroughly argued in the Codex committee concerned;

   (d) to ensure, as far as practicable, that delegations are given sufficient warning of amendments so that they may brief themselves adequately,

amendments to Codex standards at Step 8 should, as far as practicable, be submitted in writing, although amendments proposed in the Commission would not be excluded entirely, and the following procedure should be employed:

2. When Codex standards are distributed to Member Countries prior to their consideration by the Commission at Step 8, the Secretariat will indicate the date by which proposed amendments must be received; this date will be fixed so as to allow sufficient time for such amendments to be in the hands of governments not less than one month before the session of the Commission.

3. Governments should submit amendments in writing by the date indicated and should state that they had been previously submitted to the appropriate Codex committee with details of the submission of the amendment or should give the reason why the amendment had not been proposed earlier, as the case may be.

4. When amendments are proposed during a session of the Commission, without prior notice, to a standard which is at Step 8, the Chairperson of the Commission, after consultation with the chairperson of the appropriate committee, or, if the chairperson is not present, with the delegate of the chairing country, or, in the case of subsidiary bodies which do not have a chairing country, with other appropriate persons, shall rule whether such amendments are substantive.

5. If an amendment ruled as substantive is agreed to by the Commission, it shall be referred to the appropriate Codex committee for its comments and, until such comments have been received and considered by the Commission, the standard shall not be advanced beyond Step 8 of the Procedure.

6. It will be open to any Member of the Commission to draw to the attention of the Commission any matter concerning the possible implications of a draft standard for its economic interests, including any such matter which has not, in that Member's opinion, been satisfactorily resolved at an earlier step in the Procedure for the Elaboration of Codex Standards. All the information pertaining to the matter, including the outcome of any previous consideration by the Commission or a subsidiary body thereof should be presented in writing to the Commission, together with any draft amendments to the standard which would in the opinion of the country concerned, take into account the economic implications. In considering statements concerning economic implications the Commission should have due regard to the purposes of the Codex Alimentarius concerning the protection of the health of consumers and the ensuring of fair practices in the food trade, as set forth in the General Principles of the Codex Alimentarius, as well as the economic interests of the Member concerned. It will be open

to the Commission to take any appropriate action including referring the matter to the appropriate Codex committee for its comments.

GUIDE TO THE PROCEDURE FOR THE REVISION AND AMENDMENT OF CODEX STANDARDS

1. Proposals for the amendment or revision of Codex standards should be submitted to the Commission's Secretariat in good time (not less than three months) before the session of the Commission at which they are to be considered. The proposer of an amendment should indicate the reasons for the proposed amendment and should also state whether the proposed amendment had been previously submitted to and considered by the Codex committee concerned and/or the Commission. If the proposed amendment has already been considered by the Codex committee and/or Commission, the outcome of the consideration of the proposed amendment should be stated.

2. Taking into account such information regarding the proposed amendment, as may be supplied in accordance with paragraph 1 above, and the outcome of the on-going critical review conducted by the Executive Committee, the Commission will decide whether the amendment or revision of a standard is necessary. If the Commission decides in the affirmative, and the proposer of the amendment is other than a Codex committee, the proposed amendment will be referred for consideration to the appropriate Codex committee, if such committee is still in existence. If such committee is not in existence, the Commission will determine how best to deal with the proposed amendment. If the proposer of the amendment is a Codex committee, it would be open to the Commission to decide that the proposed amendment be circulated to governments for comments prior to further consideration by the sponsoring Codex Committee. In the case of an amendment proposed by a Codex Committee, it will also be open to the Commission to adopt the amendment at Step 5 or Step 8 as appropriate, where in its opinion the amendment is either of an editorial nature or of a substantive nature but consequential to provisions in similar standards adopted by it at Step 8.

3. The procedure for amending or revising a Codex standard would be as laid down in paragraphs 5 and 6 of the Introduction to the Procedure for the Elaboration of Codex Standards.

4. When the Commission has decided to amend or revise a standard, the unrevised standard will remain the applicable Codex standard until the revised standard has been adopted by the Commission.

ARRANGEMENTS FOR THE AMENDMENT OF CODEX STANDARDS ELABORATED BY CODEX COMMITTEES WHICH HAVE ADJOURNED SINE DIE

1. The need to consider amending or revising adopted Codex standards arises from time to time for a variety of reasons amongst which can be:

(a) changes in the evaluation of food additives, pesticides and contaminants;

(b) finalization of methods of analysis;

(c) editorial amendments of guidelines or other texts adopted by the Commission and related to all or a group of Codex standards e.g. "Guidelines on Date Marking", "Guidelines on Labelling of Non-retail Containers", "Carry-over Principle";

(d) consequential amendments to earlier Codex standards arising from Commission decisions on currently adopted standards of the same type of products;

(e) consequential and other amendments arising from either revised or newly elaborated Codex standards and other texts of general applicability which have been referenced

in other Codex standards (Revision of General Principles of Food Hygiene, Codex Standard for the Labelling of Prepackaged Foods);

(f) technological developments or economic considerations e.g. provisions concerning styles, packaging media or other factors related to composition and essential quality criteria and consequential changes in labelling provisions;

2. The "Guide to the Procedure for the Revision and Amendment of Codex Standards" covers sufficiently amendments to Codex standards which have been elaborated by still active Codex Committees. In the case of amendments proposed to Codex standards elaborated by Codex Committees which have adjourned *sine die*, the procedure places an obligation on the Commission to "determine how best to deal with the proposed amendment". In order to facilitate consideration of such amendments, the Commission has established more detailed guidance within the existing procedure for the amendment and revision of Codex standards.

3. In the case where Codex committees have adjourned *sine die*:

(a) the Secretariat keeps under review all Codex standards originating from Codex Committees adjourned *sine die* and to determine the need for any amendments arising from decisions of the Commission, in particular amendments of the type mentioned in para. 1(a), (b), (c), (d) and those of (e) if of an editorial nature. If a need to amend the standard appears appropriate then the Secretariat should prepare a text for adoption in the Commission;

(b) amendments of the type in para (f) and those of (e) of a substantive nature, the Secretariat in cooperation with the national secretariat of the adjourned Committee and, if possible, the Chairperson of that Committee, should agree on the need for such an amendment and prepare a working paper containing the wording of a proposed amendment and the reasons for proposing such amendment, and request comments from Member Governments: (a) on the need to proceed with such an amendment and (b) on the proposed amendment itself. If the majority of the replies received from Member Governments is affirmative on both the need to amend the standard and the suitability of the proposed wording for the amendment or an alternative proposed wording, the proposal should be submitted to the Commission with a request to approve the amendment of the standard concerned. In cases where replies do not appear to offer an uncontroversial solution then the Commission should be informed accordingly and it would be for the Commission to determine how best to proceed.

ANNEX 2

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (CX-730)

Host Government: United States of America

Sessions:

1st Washington, D.C. 27-31 October, 1986

2nd Washington, D.C. 30 November - 4 December 1987

3rd Washington, D.C. 31 October - 4 November 1988

4th Washington, D.C. 24-27 October 1989

5th Washington, D.C. 16-19 October 1990

6th Washington, D.C. 22-25 October 1991

7th Washington, D.C., 20-23 October 1992

8th Washington, D.C., 7-10 June 1994

9th Washington, D.C., 5-8 December 1995

10th San José (Costa Rica), 29 October - 1 November 1996

11th Washington D.C., 15-18 September 1998

12th Washington, D.C., 28-31 March 2000

13th Charleston, South Carolina, 4 - 7 December 2001

14th Arlington, Virginia, 4-7 March 2003

15th Alexandria, Virginia, 26-29 October 2004

Terms of reference:

(a) to determine priorities for the consideration of residues of veterinary drugs in foods;

(b) to recommend maximum levels of such substances;

(c) to develop codes of practice as may be required;

(d) to consider methods of sampling and analysis for the determination of veterinary drug residues in foods.

(Extract from the Procedural Manual, 15th Edition)

ANNEX 3

MEASURES TO FACILITATE CONSENSUS[6]

The Codex Alimentarius Commission desiring that every effort should be made to reach agreement on the adoption or amendment of standards by consensus, recommends the following measures to facilitate consensus:

- Refraining from submitting proposals in the step process where the scientific basis is not well established on current data and, where necessary, carry out further studies in order to clarify controversial issues;

- Providing for thorough discussions and documentation of the issues at meetings of the committees concerned;

- Organizing informal meetings of the parties concerned where disagreements arise, provided that the objectives of any such meetings are clearly defined by the Committee concerned and that participation is open to all interest delegations and observers in order to preserve transparency;

- Redefining, where possible, the scope of the subject matter being considered for the elaboration of standards in order to cut out issues on which consensus could not be reached;

- Providing that matters are not progressed from step to step until all relevant concerns are taken into account and adequate compromises worked out;

- Emphasizing to Committees and their Chairpersons that matters should not be passed on to the Commission until such time as consensus has been achieved at the technical level;

- Facilitating the increased involvement and participation of developing countries.

[6] Decision of the 26th Session of the Commission, 2003.

ANNEX 4

GENERAL PRINCIPLES OF THE CODEX ALIMENTARIUS[7]

PURPOSE OF THE CODEX ALIMENTARIUS

1. The Codex Alimentarius is a collection of internationally adopted food standards presented in a uniform manner. These food standards aim at protecting consumers' health and ensuring fair practices in the food trade. The Codex Alimentarius also includes provisions of an advisory nature in the form of codes of practice, guidelines and other recommended measures intended to assist in achieving the purposes of the Codex Alimentarius. The publication of the Codex Alimentarius is intended to guide and promote the elaboration and establishment of definitions and requirements for foods to assist in their harmonization and in doing so to facilitate international trade.

SCOPE OF THE CODEX ALIMENTARIUS

2. The Codex Alimentarius includes standards for all the principle foods, whether processed, semi-processed or raw, for distribution to the consumer. Materials for further processing into foods should be included to the extent necessary to achieve the purposes of the Codex Alimentarius as defined. The Codex Alimentarius includes provisions in respect of food hygiene, food additives, pesticide residues, contaminants, labelling and presentation, methods of analysis and sampling. It also includes provisions of an advisory nature in the form of codes of practice, guidelines and other recommended measures.

NATURE OF CODEX STANDARDS

3. Codex standards contain requirements for food aimed at ensuring for the consumer a sound, wholesome food product free from adulteration, correctly labelled and presented. A Codex standard for any food or foods should be drawn up in accordance with the Format for Codex Commodity Standards and contain, as appropriate, the criteria listed therein.

ACCEPTANCE OF CODEX COMMODITY STANDARDS

4.A. A Codex standard may be accepted by a country in accordance with its established legal and administrative procedures in respect of distribution of the product concerned, whether imported or home produced, within its territorial jurisdiction in the following ways:

(i) Full acceptance

(a) Full acceptance means that the country concerned will ensure that a product to which the standard applies will be permitted to be distributed freely, in accordance with (c) below, within its territorial jurisdiction under the name and description laid down in the standard, provided that it complies with all the relevant requirements of the standard.

(b) The country will also ensure that products not complying with the standard will not be permitted to be distributed under the name and description laid down in the standard.

(c) The distribution of any sound products conforming with the standard will not be hindered by any legal or administrative provisions in the country concerned relating to the health of the

[7] Procedural Manual of the Codex Alimentarius Commission (14th Edition).

consumer or to other food standard matters except for considerations of human, plant or animal health which are not specifically dealt with in the standard.

(ii) Acceptance with specified deviations

Acceptance with specified deviations means that the country concerned gives acceptance, as defined in paragraph 4.A(i), to the standard with the exception of such deviations as are specified in detail in its declaration of acceptance; it being understood that a product complying with the standard as qualified by these deviations will be permitted to be distributed freely within the territorial jurisdiction of the country concerned. The country concerned will further include in its declaration of acceptance a statement of the reasons for these deviations, and also indicate:

(a) whether products fully conforming to the standard may be distributed freely within its territorial jurisdiction in accordance with paragraph 4.A(i);

(b) whether it expects to be able to give full acceptance to the standard and, if so, when.

(iii) Free distribution

A declaration of free distribution means that the country concerned undertakes that products conforming with a Codex commodity standard may be distributed freely within its territorial jurisdiction insofar as matters covered by the Codex commodity standard are concerned.

B. A country which considers that it cannot accept the standard in any of the ways mentioned above should indicate:

(i) whether products conforming to the standard may be distributed freely within its territorial jurisdiction;

(ii) in what ways its present or proposed requirements differ from the standard, and, if possible the reasons for these differences.

C. (i) A country which accepts a Codex standard according to one of the provisions of 4.A is responsible for the uniform and impartial application of the provisions of the standard as accepted, in respect of all home-produced and imported products distributed within its territorial jurisdiction. In addition, the country should be prepared to offer advice and guidance to exporters and processors of products for export to promote understanding of and compliance with the requirements of importing countries which have accepted a Codex standard according to one of the provisions of 4.A.

(ii) Where, in an importing country, a product claimed to be in compliance with a Codex standard is found not to be in compliance with that standard, whether in respect of the label accompanying the product or otherwise, the importing country should inform the competent authorities in the exporting country of all the relevant facts and in particular the details of the origin of the product in question (name and address of the exporter), if it is thought that a person in the exporting country is responsible for such non-compliance.

ACCEPTANCE OF CODEX GENERAL STANDARDS

5.A. A Codex general standard may be accepted by a country in accordance with its established legal and administrative procedures in respect of the distribution of products to which the general standard applies, whether imported or home-produced, within its territorial jurisdiction in the following ways:

(i) Full acceptance

Full acceptance of a general standard means that the country concerned will ensure, within its territorial jurisdiction, that a product to which the general standard applies will comply with all the relevant requirements of the general standard except as otherwise provided in a Codex commodity standard. It also means that the distribution of any sound products conforming with the standard will not be hindered by any legal or administrative provisions in the country concerned, which relate to the health of the consumer or to other food standard matters and which are covered by the requirements of the general standard.

(ii) Acceptance with specified deviations

Acceptance with specified deviations means that the country concerned gives acceptance, as defined in paragraph 5.A(i), to the general standard with the exception of such deviations as are specified in detail in its declaration of acceptance. The country concerned will further include in its declaration of acceptance a statement of the reasons for these deviations, and also indicate whether it expects to be able to give full acceptance to the general standard and, if so, when.

(iii) Free distribution

A declaration of free distribution means that the country concerned undertakes that products conforming with the relevant requirements of a Codex general standard may be distributed freely within its territorial jurisdiction insofar as matters covered by the Codex general standard are concerned.

B. A country which considers that it cannot accept the general standard in any of the ways mentioned above should indicate in what ways its present or proposed requirements differ from the general standard, and if possible, the reasons for these differences.

C. (i) A country which accepts a general standard according to one of the provisions of paragraph 5.A is responsible for the uniform and impartial application of the provisions of the standard as accepted, in respect of all home produced and imported products distributed within its territorial jurisdiction. In addition, the country should be prepared to offer advice and guidance to exporters and processors of products for export to promote understanding of and compliance with the requirements of importing countries which have accepted a general standard according to one of the provisions of paragraph 5.A.

(ii) Where, in an importing country, a product claimed to be in compliance with a general standard is found not to be in compliance with that standard, whether in respect of the label accompanying the product or otherwise, the importing country should inform the competent authorities in the exporting country of all the relevant facts and in particular the details of the origin of the product in question (name and address of the exporter), if it is thought that a person in the exporting country is responsible for such non-compliance.

ACCEPTANCE OF CODEX MAXIMUM LIMITS FOR RESIDUES OF PESTICIDES AND VETERINARY DRUGS IN FOOD

6.A. A Codex maximum limit for residues of pesticides or veterinary drugs in food may be accepted by a country in accordance with its established legal and administrative procedures in respect of the distribution within its territorial jurisdiction of (a) home-produced and imported food or (b) imported food only, to which the Codex maximum limit applies in the ways set forth below. In addition, where a Codex maximum limit applies to a group of foods not individually named, a country

accepting such Codex maximum limit in respect of other than the group of foods, shall specify the foods in respect of which the Codex maximum limit is accepted.

(i) Full acceptance

Full acceptance of a Codex maximum limit for residues of pesticides or veterinary drugs in food means that the country concerned will ensure, within its territorial jurisdiction, that a food, whether home-produced or imported, to which the Codex maximum limit applies, will comply with that limit. It also means that the distribution of a food conforming with the Codex maximum limit will not be hindered by any legal or administrative provisions in the country concerned which relate to matters covered by the Codex maximum limit.

(ii) Free distribution

A declaration of free distribution means that the country concerned undertakes that products conforming with the Codex maximum limit for residues of pesticides or veterinary drugs in food may be distributed freely within its territorial jurisdiction insofar as matters covered by the Codex maximum limit are concerned.

B. A country which considers that it cannot accept the Codex maximum limit for residues of pesticides or veterinary drugs in foods in any of the ways mentioned above should indicate in what ways its present or proposed requirements differ from the Codex maximum limit and, if possible, the reasons for these differences.

C. A country which accepts a Codex maximum limit for residues of pesticides or veterinary drugs in food according to one of the provisions of paragraph 6.A should be prepared to offer advice and guidance to exporters and processors of food for export to promote understanding of and compliance with the requirements of importing countries which have accepted a Codex maximum limit according to one of the provisions of paragraph 6.A.

D. Where, in an importing country, a food claimed to be in compliance with a Codex maximum limit is found not to be in compliance with the Codex maximum limit, the importing country should inform the competent authorities in the exporting country of all the relevant facts and, in particular, the details of the origin of the food in question (name and address of the exporter), if it is thought that a person in the exporting country is responsible for such non-compliance.

WITHDRAWAL OR AMENDMENT OF ACCEPTANCE

7. The withdrawal or amendment of acceptance of a Codex standard or a Codex maximum limit for residues of pesticides or veterinary drugs in food by a country shall be notified in writing to the Codex Alimentarius Commission's Secretariat who will inform all Member States and Associate Members of FAO and WHO of the notification and its date of receipt. The country concerned should provide the information required under paragraphs 4.A(iii), 5.A(iii), 4.B, 5.B or 6.B above, whichever is appropriate. It should also give as long a notice of the withdrawal or amendment as is practicable.

REVISION OF CODEX STANDARDS

8. The Codex Alimentarius Commission and its subsidiary bodies are committed to revision as necessary of Codex standards and related texts to ensure that they are consistent with and reflect current scientific knowledge and other relevant information. When required, a standard or related text shall be revised or removed using the same procedures as followed for the elaboration of a new standard. Each member of the Codex Alimentarius Commission is responsible for identifying, and

presenting to the appropriate committee, any new scientific and other relevant information which may warrant revision of any existing Codex standards or related texts.

GUIDELINES FOR THE ACCEPTANCE PROCEDURE FOR CODEX STANDARDS

THE IMPORTANCE OF A RESPONSE TO EVERY NOTIFICATION

1. The Codex Alimentarius is the record of Codex Standards and of acceptances or other notifications by Member Countries or international organizations to which competence in the matter has been transferred by their Member States. It is revised regularly to take account of the issue of new or amended standards and the receipt of notifications. It is important that governments respond to every issue of new or amended standards. Governments should aim at giving formal acceptance to the standards. If acceptance or free circulation cannot be given unconditionally, the deviations or conditions, and the reasons, can be included in the response. Early and regular responses will ensure that the Codex Alimentarius can be kept up to date so as to serve as an indispensable reference for governments and international traders.

2. Governments should ensure that the information in the Codex Alimentarius reflects the up to date position. When changing national laws or practices the need for a notification to the Codex Secretariat should always be kept in mind.

3. The Codex procedure for elaboration of standards enables governments to participate at all stages. Governments should be able to make an early response to the issue of a Codex standard and should do their utmost to be ready to do so.

THE CODEX ALIMENTARIUS: NOT A SUBSTITUTE FOR, OR ALTERNATIVE TO, REFERRING TO NATIONAL LEGISLATION

4. Every country's laws and administrative procedures contain provisions which it is essential to understand and comply with. It is usually the practice to take steps to obtain copies of relevant legislation and/or to obtain professional advice about compliance. The Codex Alimentarius is a comparative record of the substantive similarities and differences between Codex Standards and corresponding national legislation. The Codex Standard will not normally deal with general matters of human, plant or animal health or with trade marks. The language which is required on labels will be a matter for national legislation and so will import licences and other administrative procedures.

5. The responses by governments should show clearly which provisions of the Codex Standard are identical to, similar to or different from, the related national requirements. General statements that national laws must be complied with should be avoided or accompanied by details of national provisions which require attention. Judgement will sometimes be required where the national law is in a different form or where it has different provisions.

OBLIGATIONS UNDER THE ACCEPTANCE PROCEDURE

6. The obligations which a country undertakes under the acceptance procedure are included in paragraph 4 of the General Principles. Paragraph 4.A(i)(a) provides for free distribution of conforming products, 4.A(i)(b) with the need to ensure that products which do not conform may not be distributed "under the name and description laid down". Paragraph 4.A(i)(c) is a general requirement not to hinder the distribution of sound products, except for matters relating to human, plant or animal health, not specifically dealt with in the standard. Similar provisions are included in Acceptance with Specified Deviations.

7. The essential difference between acceptances and notifications of free distribution is that a country which accepts, undertakes to enforce the Codex standard and to accept all the obligations set out in the General Principles subject to any specified deviations.

8. The Codex Committee on General Principles (CCGP) and the Commission (CAC) have reviewed the acceptance procedure and notifications by governments on a number of occasions. While recognizing that difficulties can arise from time to time in reconciling the obligations of the acceptance procedure with the laws and administrative procedures of a Member Country, the CCGP and the CAC have determined that the obligations are essential to the work and status of the CAC and that they should not be weakened in any way. The purpose of these guidelines therefore is to assist governments when they are considering how, in the light of the objectives of the acceptance procedure, to respond to Codex Standards.

THE RETURN OF THE RESPONSE

9. The principal decision which is required is whether to notify an acceptance according to one of the methods prescribed, or non acceptance as provided for in 4.B. Free distribution (4.A(iii)) does not carry with it the obligation to prevent non conforming products from being circulated, and it may be useful in cases where there is no corresponding national standard and no intention to introduce one.

THE NEED FOR AN INFORMED, RESPONSIBLE JUDGEMENT WHEN COMPARING THE CODEX STANDARD WITH NATIONAL LAWS

10. There will be some occasions when the detail in the Codex Standard is identical with national laws. Difficulties will arise however when national laws are in a different form, contain different figures or no figures at all, or in cases where there may be no standard in the country which corresponds in substance to the Codex Standard. The authority responsible for notifying the response to the CAC is urged to do its best to overcome any such difficulties by the exercise of its best endeavours and to respond, after such consultations as may be appropriate with the national organizations. The grounds on which the judgement has been based can be made clear in the notification. It may well be that they will not be such as to justify an acceptance, because of the obligations to stop the distribution of non conforming products, but a statement of free circulation should be possible on the basis of the facts and practices of each case. If there was a court decision or change in the law or practice subsequently, an amending response should be made.

PRESUMPTIVE STANDARDS

11. A presumptive standard is one which is assumed to be the standard in the absence of any other. (A presumption in law is the assumption of the truth of anything until the contrary is proved.) Some countries have said that a Codex MRL is the presumptive limit for a pesticide residue. Countries may be able and willing to regard a Codex Standard as the presumptive standard in cases where there is no corresponding standard, code of practice or other accepted expression of the "nature, substance or quality" of the food. A country need not apply the presumption to all the provisions of the standard if the details of its additives, contaminants, hygiene or labelling rules are different from those in the standard. In such a case the provisions in the Codex Standard defining the description, essential composition and quality factors relating to the specified name and description could still be the presumptive standard for those matters.

12. The justification for regarding the Codex Standard as a presumptive standard is the fact that it is the minimum standard for a food elaborated in the CAC "so as to ensure a sound, wholesome product free from adulteration, correctly labelled and presented". (General Principles, Paragraph 3.) The word minimum does not have any pejorative connotations: it simply means the level of quality

and soundness of a product judged by consensus to be appropriate for trade internationally and nationally.

13. Whether a presumptive standard would merit an acceptance would depend on whether the country concerned could say that non conforming products could not be distributed under the same name and description laid down in the standard. However it would enable a declaration of free circulation to be made and countries are asked to give the idea serious consideration.

FORMAT AND CONTENT OF CODEX STANDARDS

Scope

14. This section, together with the name of the standard and the name and description laid down in the labelling section, should be examined in order to assess whether the obligations of the acceptance procedure can properly be accepted.

Description, essential composition and quality factors

15. These sections will define the minimum standard for the food. They will be the most difficult to address unless by chance the details are virtually identical (i.e. ignoring significant matters of editorial expression or format). However, a country which has taken part in the elaboration of the standard either by attending the meetings or by sending comments under the Step Procedure has, no doubt, consulted national organizations on the extent to which the draft provisions in the standard would be acceptable nationally. This factual information needs to be turned into a formal response when the standard is sent out for acceptance. Countries are asked to do their best to exercise an informal judgement on lines discussed in Paragraph 7 above. Some of the quality criteria e.g. allowances for defects may represent good manufacturing practice or be left to trade contracts. This will have to be taken into account. A free distribution response ought to be possible in most cases.

Food Additives

16. The food additives included in the standard have been assessed and cleared by JECFA. The Commodity Committee and the CCFAC have assessed technological need and safety in use. If national laws are different, all the detailed differences should be reported. It should be borne in mind, however, that the aim of international food standardization work is to harmonize policies and attitudes as much as possible. Therefore every effort should be made to keep deviations to the minimum.

Contaminants

17. If national limits apply they should be quoted if not the same as those laid down in the Codex Standard. Where general laws about safety, health or nature of the food apply, the limits quoted in the standard could properly be regarded as representing those which are unavoidable in practice and within safety limits.

Hygiene and Weights and Measures

18. If national requirements are different they should be reported.

Labelling

19. The General Standard for the Labelling of Prepackaged Foods represents the international consensus on information to be included on the labels of all foods.

20. Governments are exhorted to use the General Standard as a basis for their national legislation and to keep differences to an absolute minimum especially those of detail or minutiae. Governments should observe the footnote to the Scope section and should ensure that all compulsory provisions relating to presentation of information which are additional to, and different from, those in the standard should be notified. Any other compulsory provisions in national legislation should also be notified if they are not provided for in the Codex standard. The labelling provisions in Codex standards include sections of the revised General Standard by reference. When accepting a Codex commodity standard, a country which has already accepted and responded to the General Standard can then refer to the terms of that acceptance in any subsequent responses. As much specific information as is relevant and helpful should be given. In particular, this should include the name and description relating to the food, the interpretation of any special requirements relating to the law or custom of the country, any additional details about presentation of the mandatory information and detailed differences if any in the labelling requirements e.g. in relation to class names, declaration of added water, declaration of origin. It will be assumed that the language(s) in which the particulars should be given will be as indicated by national legislation or custom.

Methods of Analysis and Sampling

21. The obligations which a country assumes in accepting the following Codex Defining Methods of Analysis included in Codex standards are as follows[8]:

(a) Codex Defining Methods of Analysis (Type I) are subject to acceptance by governments just as are the provisions which they define and which form part of Codex standards.

"Full acceptance" of a Codex Defining Method means the acceptance that the value provided for in a Codex standard is defined by means of the Codex method. In determining compliance with the value in the Codex standard, governments undertake to use the Codex Defining Method, especially in cases of disputes involving the results of analysis.

"Non acceptance" of Codex Defining Method or acceptance of Codex standards with substantive deviations in the Codex Defining Methods means acceptance of the Codex standard with specified deviation.

(b) The "acceptance" of Codex standards containing Codex Reference Methods of Analysis (Type II) means the recognition that Codex Reference Methods are methods the reliability of which has been demonstrated on the basis of internationally acceptable criteria. They are, therefore, obligatory for use, i.e. subject to acceptance by governments, in disputes involving the results of analysis. "Non acceptance" of the Codex Reference Method or acceptance of Codex standards with substantive deviations in the Codex Reference Methods for use in disputes involving methods of analysis, should be taken to mean acceptance of the Codex standard with specified deviation.

(c) The "acceptance" of Codex standards containing Codex Alternative Approved Methods of Analysis (Type III) means the recognition that Codex Alternative Approved Methods are methods the reliability of which has been demonstrated in

[8] The Committee on General Principles, when elaborating these Guidelines, noted that the Classification of Methods was under review by the Codex Committee on Methods of Analysis and Sampling and that the application of Part (b) particularly could be unnecessarily restrictive.

terms of internationally acceptable criteria. They are recommended for use in food control, inspection or for regulatory purposes.

"Non acceptance" of a Codex Alternative Approved Method does not constitute a deviation from the Codex standard.

(d) Since the reliability of the Tentative Methods (Type IV) has not yet been endorsed by the Codex Committee on Methods of Analysis and Sampling on the basis of the internationally accepted criteria, it follows that they cannot be regarded as final Codex methods. Type IV methods may, eventually become Type I, II or III methods with the resultant implications regarding the acceptance of Codex methods. Type IV methods are, therefore, not recommended as Codex methods until their reliability has been recognized by the CCMAS. They may be included in draft Codex standards or in Codex standards provided their non approved status is clearly indicated.

SUMMARY

22. Governments are urged to respond to every issue of Codex standards. The inclusion of responses in the Codex Alimentarius will enable the CAC and Member Governments to address the question of closer approximation of international and national requirements. Governments are urged to take the Codex standard fully into consideration when changing their national laws. The Codex Alimentarius will always be an invaluable reference for governments and for international traders although national legislation must always be consulted and complied with.

ANNEX 5

SPS Committee's clarification "how the Committee would differentiate standards, guidelines or recommendations in relation to the implementation of the SPS Agreement"

Geneva, 19 March 1998

Dear Mr. Orriss,

Your letter of 29 September 1997 was discussed by the Committee on Sanitary and Phytosanitary Measures ("the Committee") at its meetings of October 1997 and March 1998. The Committee instructed me to forward to you the following response.

By way of background, it must be clearly understood that the Committee cannot formally interpret the provisions of the SPS Agreement. This can be done only by the WTO Ministerial Conference or General Council, or indirectly through the dispute settlement process with regard to particular cases. Nonetheless, the Committee is required to carry out the functions necessary to implement the Agreement and the furtherance of its objectives and thus may express views, where appropriate, on the meaning of particular terms and provisions of the Agreement.

With respect to your first question on "how the Committee would differentiate standards, guidelines or recommendations in relation to the implementation of the SPS Agreement", Annex A of the SPS Agreement defines *international standards, guidelines and recommendations* as follows:

"(a) for food safety, the standards, guidelines and recommendations established by the Codex Alimentarius Commission relating to food additives, veterinary drug and pesticide residues, contaminants, methods of analysis and sampling, and codes and guidelines of hygienic practice; ..."

This definition makes no distinction between standards, guidelines and recommendations. The SPS Agreement does not provide specific definitions for the terms "standards", "guidelines" or "recommendations".

Throughout the text of the SPS Agreement, the terms "international standards, guidelines or recommendations" always appear together. Article 3.1 of the SPS Agreement states that "[t]o harmonize sanitary and phytosanitary measures on as wide a basis as possible, Members shall base their sanitary or phytosanitary measures on international standards, guidelines or recommendations ...". Article 3.2 indicates that sanitary measures which "... conform to international standards, guidelines or recommendations shall be deemed to be necessary to protect human, animal or plant life or health, and presumed to be consistent with the relevant provisions of this Agreement ... ". Article 3.3 provides that "Members may introduce or maintain sanitary or phytosanitary measures which result in a higher level of sanitary or phytosanitary protection than would be achieved by measures based on the relevant international standards, guidelines or recommendations, if there is a scientific justification ...". In no case do these provisions differentiate between the three terms "standards", "guidelines" or "recommendations".

The Committee noted that there is no legal obligation on Members to apply Codex standards, guidelines and recommendations and, in accordance with the terms of Article 3 of the SPS Agreement, Members may choose to apply them or not. The Committee observed that how a Codex text was applied depended on its substantive content rather than the category of that text (e.g., commodity standards, MRLs, codes of practice, guidelines). This might have some bearing on how a Member could show that its measure is based on an international standard, guideline or recommendation in the context of Article 3 of the SPS Agreement. For example, a Codex standard, such as an MRL which represented a specific numeric value, may provide a higher degree of precision

than much of the content of a guideline or other Codex text. On the other hand, the Committee considered that guidelines and recommendations are intended to allow greater discretion as to the choice of measures which can be regarded as being based on the guideline or recommendation. However, the Committee was of the view that Codex work should not be constrained by this question. The Committee considers it to be an internal decision of the Codex Alimentarius Commission regarding the type and content of the texts it develops to address issues before it.

With respect to your second question on "the status the Committee would assign to Codex regional standards and related texts", in its discussions Members noted that regional standards are not included in the definition of international standards provided by Annex A of the SPS Agreement, cited above. The Committee recognized that, even if they were based on scientific evidence, regional standards were meant to apply only within a particular geographic region. However, Members do recognize that such scientifically-sound regional standards could become the foundation for the creation and adoption of international standards.

Yours sincerely,

Alex Thiermann
Chairman
Committee on Sanitary and Phytosanitary Measures

ANNEX 6

WORKING PRINCIPLES FOR RISK ANALYSIS FOR APPLICATION IN THE FRAMEWORK OF THE CODEX ALIMENTARIUS

SCOPE

1) These principles for risk analysis are intended for application in the framework of the Codex Alimentarius.

2) The objective of these Working Principles is to provide guidance to the Codex Alimentarius Commission and the joint FAO/WHO expert bodies and consultations, so that food safety and health aspects of Codex standards and related texts are based on risk analysis.

3) Within the framework of the Codex Alimentarius Commission and its procedures, the responsibility for providing advice on risk management lies with the Commission and its subsidiary bodies (risk managers), while the responsibility for risk assessment lies primarily with the joint FAO/WHO expert bodies and consultations (risk assessors).

RISK ANALYSIS - GENERAL ASPECTS

4) The risk analysis used in Codex should be:

– applied consistently;

– open, transparent and documented;

– conducted in accordance with both the *Statements of Principle Concerning the Role of Science in the Codex Decision-Making Process and the Extent to Which Other Factors are Taken into Account and the Statements of Principle Relating to the Role of Food Safety Risk Assessment*; and

– evaluated and reviewed as appropriate in the light of newly generated scientific data.

5) The risk analysis should follow a structured approach comprising the three distinct but closely linked components of risk analysis (risk assessment, risk management and risk communication) as defined by the Codex Alimentarius Commission[9], each component being integral to the overall risk analysis.

6) The three components of risk analysis should be documented fully and systematically in a transparent manner. While respecting legitimate concerns to preserve confidentiality, documentation should be accessible to all interested parties[10].

7) Effective communication and consultation with all interested parties should be ensured throughout the risk analysis.

[9] See *Definitions of Risk Analysis Terms Related to Food Safety,* Codex Alimentarius Commission Procedural Manual.

[10] For the purpose of the present document, the term "interested parties" refers to "risk assessors, risk managers, consumers, industry, the academic community and, as appropriate, other relevant parties and their representative organizations" (see definition of "Risk Communication")

8) The three components of risk analysis should be applied within an overarching framework for management of food related risks to human health.

9) There should be a functional separation of risk assessment and risk management, in order to ensure the scientific integrity of the risk assessment, to avoid confusion over the functions to be performed by risk assessors and risk managers and to reduce any conflict of interest. However, it is recognized that risk analysis is an iterative process, and interaction between risk managers and risk assessors is essential for practical application.

10) When there is evidence that a risk to human health exists but scientific data are insufficient or incomplete, the Codex Alimentarius Commission should not proceed to elaborate a standard but should consider elaborating a related text, such as a code of practice, provided that such a text would be supported by the available scientific evidence.[11]

11) Precaution is an inherent element of risk analysis. Many sources of uncertainty exist in the process of risk assessment and risk management of food related hazards to human health. The degree of uncertainty and variability in the available scientific information should be explicitly considered in the risk analysis. Where there is sufficient scientific evidence to allow Codex to proceed to elaborate a standard or related text, the assumptions used for the risk assessment and the risk management options selected should reflect the degree of uncertainty and the characteristics of the hazard.

12) The needs and situations of developing countries should be specifically identified and taken into account by the responsible bodies in the different stages of the risk analysis.

RISK ASSESSMENT POLICY

13) Determination of risk assessment policy should be included as a specific component of risk management.

14) Risk assessment policy should be established by risk managers in advance of risk assessment, in consultation with risk assessors and all other interested parties. This procedure aims at ensuring that the risk assessment is systematic, complete, unbiased and transparent.

15) The mandate given by risk managers to risk assessors should be as clear as possible.

16) Where necessary, risk managers should ask risk assessors to evaluate the potential changes in risk resulting from different risk management options.

RISK ASSESSMENT[12]

17) The scope and purpose of the particular risk assessment being carried out should be clearly stated and in accordance with risk assessment policy. The output form and possible alternative outputs of the risk assessment should be defined

18) Experts responsible for risk assessment should be selected in a transparent manner on the basis of their expertise, experience, and their independence with regard to the interests involved. The procedures used to select these experts should be documented including a public declaration of any potential conflict of interest. This declaration should also identify and detail their individual expertise, experience and independence. Expert bodies and consultations should ensure effective participation of experts from different parts of the world, including experts from developing countries.

[11] Statement adopted by the 24th Session of the Commission (ALINORM 01/41, paras. 81-83)

[12] Reference is made to the Statements *of Principle Relating to the Role of Food Safety Risk Assessment*

19) Risk assessment should be conducted in accordance with the *Statements of Principle Relating to the Role of Food Safety Risk Assessment* and should incorporate the four steps of the risk assessment, i.e. hazard identification, hazard characterization, exposure assessment and risk characterization.

20) Risk assessment should be based on all available scientific data. It should use available quantitative information to the greatest extent possible. Risk assessment may also take into account qualitative information.

21) Risk assessment should take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection and the prevalence of specific adverse health effects.

22) Risk assessment should seek and incorporate relevant data from different parts of the world, including that from developing countries. These data should particularly include epidemiological surveillance data, analytical and exposure data. Where relevant data are not available from developing countries, the Commission should request that FAO/WHO initiate time-bound studies for this purpose. The conduct of the risk assessment should not be inappropriately delayed pending receipt of these data; however, the risk assessment should be reconsidered when such data are available.

23) Constraints, uncertainties and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner. Expression of uncertainty or variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable.

24) Risk assessments should be based on realistic exposure scenarios, with consideration of different situations being defined by risk assessment policy. They should include consideration of susceptible and high-risk population groups. Acute, chronic (including long-term), cumulative and/or combined adverse health effects should be taken into account in carrying out risk assessment, where relevant.

25) The report of the risk assessment should indicate any constraints, uncertainties, assumptions and their impact on the risk assessment. Minority opinions should also be recorded. The responsibility for resolving the impact of uncertainty on the risk management decision lies with the risk manager, not the risk assessors.

26) The conclusion of the risk assessment including a risk estimate, if available, should be presented in a readily understandable and useful form to risk managers and made available to other risk assessors and interested parties so that they can review the assessment.

RISK MANAGEMENT

27) While recognizing the dual purposes of the Codex Alimentarius are protecting the health of consumers and ensuring fair practices in the food trade, Codex decisions and recommendations on risk management should have as their primary objective the protection of the health of consumers. Unjustified differences in the level of consumer health protection to address similar risks in different situations should be avoided.

28) Risk management should follow a structured approach including preliminary risk management activities[13], evaluation of risk management options, monitoring and review of the decision taken. The decisions should be based on risk assessment, and taking into account, where appropriate, other legitimate factors relevant for the health protection of consumers and for the promotion of fair practices in food trade, in accordance with the *Criteria for the Consideration of the Other Factors Referred to in the Second Statement of Principles* [14].

29) The Codex Alimentarius Commission and its subsidiary bodies, acting as risk managers in the context of these Working Principles, should ensure that the conclusion of the risk assessment is presented before making final proposals or decisions on the available risk management options, in particular in the setting of standards or maximum levels, bearing in mind the guidance given in paragraph 10.

30) In achieving agreed outcomes, risk management should take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection, feasibility of enforcement and compliance, and the prevalence of specific adverse health effects.

31) The risk management process should be transparent, consistent and fully documented. Codex decisions and recommendations on risk management should be documented, and where appropriate clearly identified in individual Codex standards and related texts so as to facilitate a wider understanding of the risk management process by all interested parties.

32) The outcome of the preliminary risk management activities and the risk assessment should be combined with the evaluation of available risk management options in order to reach a decision on management of the risk.

33) Risk management options should be assessed in terms of the scope and purpose of risk analysis and the level of consumer health protection they achieve. The option of not taking any action should also be considered.

34) In order to avoid unjustified trade barriers, risk management should ensure transparency and consistency in the decision-making process in all cases. Examination of the full range of risk management options should, as far as possible, take into account an assessment of their potential advantages and disadvantages. When making a choice among different risk management options, which are equally effective in protecting the health of the consumer, the Commission and its subsidiary bodies should seek and take into consideration the potential impact of such measures on trade among its Member countries and select measures that are no more trade-restrictive than necessary.

35) Risk management should take into account the economic consequences and the feasibility of risk management options. Risk management should also recognize the need for alternative options in the establishment of standards, guidelines and other recommendations, consistent with the protection of consumers' health. In taking these elements into consideration, the Commission and its subsidiary bodies should give particular attention to the circumstances of developing countries.

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[13] For the purpose of these Principles, preliminary risk management activities are taken to include: identification of a food safety problem; establishment of a risk profile; ranking of the hazard for risk assessment and risk management priority; establishment of risk assessment policy for the conduct of the risk assessment; commissioning of the risk assessment; and consideration of the result of the risk assessment.

[14] These criteria have been adopted by the 24th Session of the Commission (see Procedural Manual 12th Edition - Appendix, page 165)

36) Risk management should be a continuing process that takes into account all newly generated data in the evaluation and review of risk management decisions. Food standards and related texts should be reviewed regularly and updated as necessary to reflect new scientific knowledge and other information relevant to risk analysis.

RISK COMMUNICATION

37) Risk communication should:

(i) promote awareness and understanding of the specific issues under consideration during the risk analysis;

(ii) promote consistency and transparency in formulating risk management options/recommendations;

(iii) provide a sound basis for understanding the risk management decisions proposed;

(iv) improve the overall effectiveness and efficiency of the risk analysis;

(v) strengthen the working relationships among participants;

(vi) foster public understanding of the process, so as to enhance trust and confidence in the safety of the food supply;

(vii) promote the appropriate involvement of all interested parties; and

(viii) exchange information in relation to the concerns of interested parties about the risks associated with food.

38) Risk analysis should include clear, interactive and documented communication, amongst risk assessors (Joint FAO/WHO expert bodies and consultations) and risk managers (Codex Alimentarius Commission and its subsidiary bodies), and reciprocal communication with member countries and all interested parties in all aspects of the process.

39) Risk communication should be more than the dissemination of information. Its major function should be to ensure that all information and opinion required for effective risk management is incorporated into the decision making process.

40) Risk communication involving interested parties should include a transparent explanation of the risk assessment policy and of the assessment of risk, including the uncertainty. The need for specific standards or related texts and the procedures followed to determine them, including how the uncertainty was dealt with, should also be clearly explained. It should indicate any constraints, uncertainties, assumptions and their impact on the risk analysis, and minority opinions that had been expressed in the course of the risk assessment (see para.25).

41) The guidance on risk communication in this document is addressed to all those involved in carrying out risk analysis within the framework of Codex Alimentarius. However, it is also of importance for this work to be made as transparent and accessible as possible to those not directly engaged in the process and other interested parties while respecting legitimate concerns to preserve confidentiality (See para. 6).

ANNEX 7

Consideration of Risk Analysis in CCRVDF
(relevant extracts from the report of the CCRVDF)

8th Session of CCRVDF (June 1994) (ALINORM 95/31, paras 39-41)

At the request of the 20th Session of the Commission (1993) a paper entitled *Risk Assessment Procedures Used by the Codex Alimentarius Commission and its Subsidiary an Advisory Bodies* (ALINORM 93/37), prepared by a consultant Dr. S. Hathaway (New Zealand) was reviewed and discussed by the Committee.

39. The Committee supported the principles of the Hathaway paper and the view that the establishment of MRLs for residues of veterinary drugs should continued to be linked to the risk-based ADI (Acceptable Daily Intake). In this regard the Committee noted that its procedures and those of JECFA were in general consistent with the principles enunciated in the paper.

40. The Committee also agreed in principles that the use of risk analysis procedures should be extended further in the Codex Procedures for the elaboration of standards. Some delegations were of the opinion that the roles of the expert committees and the Codex committees in regard to risk assessment and risk management respectively should be clarified. However, it was noted that the overall Codex procedures had to take into account those Committees such as Food Hygiene and Meat Hygiene which did not receive independent external advise on a regular basis.

41. The Committee expressed concern at the fact that the use of the various expression used by Codex in relation to risk analysis had not been harmonised. It considered that further progress would be greatly assisted by having agreed Definitions for Codex purposes. It recommended the Executive Committee that such definitions be elaborated as a matter of priority in accordance with the new Accelerated ("Fast Track") Procedure with a view to their adoption by the CAC at its 21st Session. The Committee proposed that the definitions contained in Appendix IX to the present report should be sent to governments for comments and also considered by other relevant Codex Committees. It emphasized that any definitions adopted by the Commission should be harmonised to the extent possible with those of other relevant international organizations, for example, the OIE.

9th Session of CCRVDF (December 1995) (ALINORM 97/31, para. 14)

At its 9th Session, at the request of the 21st Session of the Commission (1995) examined the report of the Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues (Geneva, Switzerland, 13-17 March 1995).

14. The Committee supported the incorporation of a science-based approach to risk analysis into its work, and agreed that a discussion paper would be developed under the direction of France, with assistance provided by Australia, Canada, the Netherlands, New Zealand, Norway and the United States, for consideration at its 10th Session. The paper should address the possible implementation of the recommendations of the FAO/WHO Expert Consultation of the Application of Risk Analysis to Food Standards Issues as they applied to the work of CCRVDF, and to consider initiatives undertaken by other Codex Committees.

10th Session of CCRVDF (October 1996) (ALINORM 97/31A, paras 9-13)

Following the decision of its 9th Session, the 10th Session of the Committee considered the paper by France to address the implementation of the Consultation's recommendations as they applied to the work of the Committee.

9. The Committee expressed its appreciation of the thorough analysis presented in the discussion paper. It noted that the development of risk analysis in Codex and in its work was an on-going process and that the analysis presented both a report of the current status and issues which needed to be addressed in the future. It concurred with the main conclusions of the paper, namely that the process of establishing MRLs for veterinary drugs incorporated various the stages of risk assessment very well, and that a number of elements relating to risk management were integrated. It noted that the recommendation made by the 1995 Joint FAO/WHO Expert Consultation to separate the risk assessment and the risk management processes was therefore not being currently followed in this process.

10. To the extent that it was possible to control strictly the conditions under which veterinary drugs were used, and food taken from treated animals could be collected, the Committee considered whether the results of the MRL-setting process was not so much as to evaluate a risk which would be socially acceptable, but to minimize risks associated with the presence of drug residues in food stuffs. However, the Committee further recognised the need to delineate more fully the risk assessment and the risk management of the process, and noted that government regulatory agencies and other played a major role in risk management of drug residues in foods.

11. The Committee identified several issues which required further attention, specifically:

- Better delineation of the respective roles of the Committee and JECFA;
- Improvement of transparency of the process;
- Recognition that the application of safety factors and other conventions to address uncertainty were not strictly scientifically based and therefore introduced an element of risk management into the risk assessment process;
- Consideration of the benefits of the use of veterinary drugs as well as risks, for animals as well as humans;
- Problems in relation to animal studies and the potential of using in vitro studies as alternative for such studies;
- Problems related to the generation of residue data for minor species, and;
- Problems related to old substances which had not been evaluated under modern criteria, but which were still in use in many countries, and substances on the so-called "inactive list".

12. The Committee agreed to refer its main findings to the Commission, but noting the forthcoming Expert Consultations of the Application of Risk management to Food safety Matters (Rome 28-31 January 1997) and on Food Consumption and Risk Assessment (Geneva, 10-14 February 1997), indicated its intention to circulate a revised paper for comments incorporating the issues raised at the present session and the outcome of these Consultations and of the Commission's deliberations. In the meantime, delegations were encouraged to send comments on the

discussion paper directly to the Delegation of France. The Committee welcomed the offer of the French Delegation to revise the document accordingly.

13. The Committee agreed to review developments in risk analysis at its next Session following consideration of this matter by the Commission.

11th Session of CCRVDF (September 1998) (ALINORM 99/31, paras 43-44)

At its 11th Session, the Committee considered the revised "Discussion paper on Risk Analysis in the Codex Committee on Residues of Veterinary Drugs in Foods" (CX/RVDF 98/4)

43. The revised paper was presented by Dr J. Boisseau (France). He noted that the paper had been expanded to take into account the recommendations of the FAO/WHO consultations, particularly those on risk management and risk communication. He reviewed the three elements of risk analysis as they pertain to this Committee and in particular, noted that issues related to risk assessment would require the development of risk assessment policies., In the interest of transparency, these policies should be made explicit.

44. Several delegations congratulated the French Delegation on its excellent work. Due to the late availability of the document, an in-depth discussion of the paper was not possible, The Committee agreed to append the document to its report (see Appendix IX) for circulation and comments, with the understanding that France would take the lead in revision the paper on the basis of the above discussion and comments submitted for further consideration at its next meeting. The Delegations of the Netherlands, New Zealand, Sweden, the United Kingdom and the United States and representatives if Consumers International, COMISA, WHO and WHA agreed to assist France in this effort. In revising the paper, the Committee also requested that the document include specific risk assessment policy issues that may need to be addressed.

12th Session of CCRVDF (March 2000) (ALINORM 01/31, paras 15-19)

At its 12th Session, the Committee considered risk analysis principles and methodologies of the Codex Committee on Residues of Veterinary Drugs in Foods (CX/RVDF 00/3 "Overview and discussion on risk analysis by the 23rd Session of the Commission" and CX/RVDF 00/3, Add.1 "Risk Analysis Principles and Methodologies of the Codex Committee on Residues of Veterinary Drugs in Foods – Elaboration of a Risk Assessment Policy by the CCRVDF").

15. The Committee noted and welcomed the recommendation of the 23rd Session of the Commission in relation to principles of risk analysis addressed to the Codex Alimentarius Commission and its subsidiary bodies, governments, and FAO and WHO. Among those recommendations relevant to the work of this Committee, the Committee agreed that it would consider, pending the preparation of a discussion paper: (1) the development and application of risk analysis principles and methodologies appropriate to the specific mandate within the framework of the Action Plan; and (2) development of quality criteria for data used for risk assessment. It took note, for implementation as appropriate, of the recommendations regarding the appointment of a developing country(ies) as co-author(s) for positions papers; basing risk assessment on global data including that from developing countries; taking into account the economic consequences and the feasibility of risk management options in developing countries; and consideration of acute aspects of dietary exposure to chemicals in foods. It also took note of the recommendations to increase interaction and communication between expert bodies and the Codex Committees.

16. The Delegation of France introduces the paper CX/RVDF 00/3-Add.1. It was stated that comments had been received on the text contained in Appendix IX of ALINORM 99/31 only from Consumers International and therefore the text had not been revised. The Delegation mentioned that

the Committee had not yet established risk assessment policy which was a component of risk management and the work should be done urgently on this issue. It was proposed that since the issue was very technical and complex, in order to facilitate discussion on the plenary, a drafting group should be formed to prepare a discussion paper containing solid recommendations regarding risk analysis principles and methodologies including risk assessment policy. For this purpose, the Delegation drew the attention of the Committee to existing reference documents of JECFA relevant to the issue.

17. A number of delegations supported the creation of a drafting group. Several delegation and one observer stated that the paper prepared for the last session contained useful information that should be used as a basis for further development.

18. A delegation stated that risk management was the function of Codex Committees and national governments, the leadership in this work should be taken by this Committee; and all efforts should be made to encourage developing countries to take part in the draft. Another delegation proposed that information should be requested from all concerned on subjects to be included in the paper in addition to what has been done by JECFA.

19. The Committee agreed that a drafting group (Australia, Brazil, Canada, Chile, France, Japan, Mexico, Netherlands, New Zealand, Philippines, Poland, Sweden, Switzerland, Thailand, United States, JECFA Secretariat, European Community, OIE, WHO, Consumers International and COMISA) led by France and Poland would prepare a discussion paper for government comments well before the next session of the Committee. In order to facilitate the drafting process, member countries were invited to provide comments and information relevant to the subject to France. It was mentioned that the drafting process should be accelerated buy using modern communication technologies. It was noted that the process of drafting the paper should be as transparent as possible.

13th Session of CCRVDF (December 2001) (ALINORM 03/31, paras 65-70)

At its 13th Session, the Committee considered a document on Risk Analysis Principles and Methodologies of the Codex Committee on Residues of Veterinary Drugs in Foods (CX/RVDF 01/9) and noted the recommendation of the 24th Session of the Commission that relevant Codex committees should continue to develop and document the application of risk analysis in their work.

65. The Committee was also informed of the Commission request to FAO and WHO to convene a consultation to review the status and procedures of expert bodies and to develop recommendations for consideration by the Directors-General on additional ways to improve the quality, quantity and timeliness of scientific advice to the Commission. It was noted that this review would include the examination of increased coordination between the JECFA, JMPR and other groups devoted to microbiological contamination and biotechnology on matters including selection and establishment of a roster of experts for such bodies, including increased transparency in the process.

66. In presenting the Discussion Paper, the delegation of France noted that the document contained three major sections, namely: a background section describing the major elements of risk analysis and their relation to the mandates of CCRVDF and JECFA; Annex I – Establishment by CCRVDF of a Risk Assessment Policy for the Setting of Maximum Residue Limits for Veterinary Drugs in Foods; and, Annex II - Risk Management and Codex Procedures for Establishing MRLs of Veterinary Medicinal Products. The delegation of France noted that Annex I examined various aspects of risk assessment which need to be addressed in taking risk management decisions within the CCRVDF and contained a list of questions to JECFA to be answered at various steps of JECFA evaluation, including outstanding issues related to the harmonization of risk assessments between JECFA and JMPR as well as between CCRVDF and CCPR; the extrapolation of MRLs to minor species and the importance of criteria concerning the protection of public health and the promotion of

fair trading practices when prioritizing compounds for JECFA review. It was noted that Annex II contained four recommendations related to the uncertainty of whether or not a substance to be considered should be marketed or not; the importance of prioritizing compounds for reasons of public health protection as well as for the promotion of trade and the availability of a dossier for evaluation; the importance of the availability of JECFA reports in a timely manner; and, the elaboration of risk management principles and criteria.

67. The Committee confirmed that in undertaking its responsibilities related to risk analysis it was necessary to formulate a coherent risk assessment policy so that sound risk management decisions could be taken in the elaboration of MRLVDs and the scientific integrity of JECFA would be protected and for transparency. It was noted that notwithstanding the independence of JECFA, this would allow the Committee to take a full role in the consideration of JECFA evaluations and in this regard, it was suggested that Annex I could be examined at the next JECFA Meeting. It was noted that Annex I could provide the basis for the future development of a risk assessment policy which would facilitate discussions and relations with JECFA in the establishment of MRLVDs.

68. Although the Committee did not reach any final conclusion on Annex 1, it was decided to forward Annex I of the document to FAO and WHO, so that it would be taken into consideration in a joint project to update and consolidate principles and methodologies of risk assessment and that JECFA would review and comment back to the CCRVDF, with the understanding that these issues would be further considered by the CCRVDF at its next Session. It was noted that the review could greatly contribute to increased communication and transparency between risk assessors and managers and would help the Committee in defining risk assessment policies and risk management guidelines related to the establishment of MRLVDs.

69. The Committee generally agreed that risk management methodologies including policies for risk assessment and risk management, be drafted to address the needs of the Codex Alimentarius Commission pertaining to the activities of this Committee. The Committee concluded that the delegation of France, with the assistance of Australia, Brazil, Canada, Chile, China, Indonesia, Japan, Korea, Mexico, the Netherlands, New Zealand, Philippines, Poland, Sweden, Switzerland, Thailand, United States, CI, EC, FAO, IFAH, OIE and WHO, would elaborate an internal policy document on "Risk Management Methodologies, including Risk Assessment Policies, in the Codex Committee on Residues of Veterinary Drugs in Foods" considering Annex II of CX/RVDF 01/9 and the comments of JECFA on Annex I of CX/RVDF 01/9. It was agreed that the paper should address the written comments submitted as well as issues raised at the current meeting under agenda items 9, 11 and 13 that were relevant to risk analysis. The Committee agreed that the document should be circulated for comment and further consideration at its next meeting, and with the understanding that the policy document would remain as internal guidance to the CCRVDF.

70. It was further agreed that the drafting group would also consider risk management options for substances which were on the past agendas of JECFA but for which no ADI or MRLs had been recommended due to various reasons, including insufficient or lack of data or where no sponsor was identified.

14th Session of CCRVDF (March 2003) (ALINORM 03/31A, paras 91 and 94-96)

At its 14th Session, the Committee considered the revised discussion paper on risk management methodologies, including risk assessment policies (CX/RVDF 03/8) that described the mandate, the role of various parties with responsibilities in risk assessment and risk management and the steps of risk management in CCRVDF. The paper also provided practical recommendations to the questions raised by the CCRVDF regarding the need to accelerate the establishment of MRLVDs, the interactions between risk assessors and risk managers; the establishment of criteria and methods to propose temporary ADIs, and; the substances with no acceptable ADI and/or MRLs .

91. The Committee expressed general support for the document prepared by France as the recommendations adequately addressed issues related to the application of risk analysis policy, the efficiency of the work of CCRVDF and the proposal of Thailand. It was recommended to better specify the responsibilities of risk managers and risk assessors, their interactive mechanisms and the communication aspects in recommendations 3, 5, 6, and 7 and to highlight the primary purpose of protecting consumers health in the establishment of MRLVDs.

94. The Committee considered the further development of the discussion paper. Some delegations suggested to follow an approach similar to the Codex Committees on Pesticide Residues and on Food Additives and Contaminants and to consider the development of a dynamic document for internal use of the Committee and in consideration of the further development of specific guidelines for risk analysis.

95. The Committee agreed that a working group (lead by France, and with the assistance of Australia, Canada, China, Costa Rica, Italy, Korea, The Netherlands, New Zealand, Poland, Spain, Switzerland, Thailand, United Kingdom, United States, Consumers International, European Commission, FAO, IFAH, OIE and WHO) would prepare a revised version of the discussion paper on "Risk Management Methodologies, including Risk Assessment Policies in the Codex Committee on Residues of Veterinary Drugs in Foods" for circulation, additional comments and further consideration at its 15th Session. The Committee accepted the kind offer of the European Community to possibly host a meeting of the working group in Brussels to discuss the further development of the document.

96. The Committee agreed that the revised document should specifically address the issue of substances with no ADI and/or MRL, should take account of the above discussion, the written comments submitted at the current meeting and the comments of the 60th meeting of JECFA on Annex I of CX/RVDF 01/9.

15th Session of CCRVDF (October 2004) (ALINORM 05/28/31, paras 141-153)

At its 15th Session, the Committee considered and reviewed the internal policy document on risk management methodologies, including risk assessment policies (CX/RVDF 04/15/08), which was prepared by the drafting group on the basis of the document presented at its previous session and the comments provided by JECFA.

141. The Committee had an extensive discussion on the need for communication strategies for risk analysis. Several delegations stressed the need for better communication between risk assessors and risk managers. The Observer from Consumers International expressed the view that communication with the public was an essential aspect of risk analysis in order to ensure public confidence in the process. The Delegation of the European Community expressed the view that the document should concentrate on communication between risk assessors and risk managers and that communication with the public might be better addressed by national governments.

142. The JECFA Secretariat highlighted the importance of adequate risk communication, especially if new procedures were developed for risk analysis of veterinary drugs, and in the case of substances that currently had no ADI or MRLs.

143. The Committee agreed that risk communication strategies should be further considered in the development of the document, and noted that the section on Risk Communication in the *Working Principles for Risk Analysis in the Framework of the Codex Alimentarius* could be taken into account in the process.

144. In reply to a question on risk assessment procedures, the Representatives of FAO and WHO informed the Committee that the procedures of JECFA and JMPR were in the process of review and would be available upon completion of the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Foods, scheduled for 2005. It was noted that what constitute Good Veterinary Practices, as applied to milk withdrawal time, should be considered a component of the risk management process.

Risk Management in the CCRVDF

Identification of a Food Safety Problem

145. The Committee noted that to be consistent with the mandate of the Codex Alimentarius, food safety needs and public health concerns (paragraphs 11 and 13), trade issues of relevance for governments should also be identified.

146. The Committee noted the written comments of Argentina, which was not present at the meeting, concerning intellectual property in paragraph 12. In this respect, the Secretariat informed the Committee that the *Working Principles for Risk Analysis in the Framework of the Codex Alimentarius* (paragraph 6) addressed the issue of confidentiality as related to the accessibility of documentation.

147. Some delegations and the Observer from IFAH expressed the view that what constituted "documentation" for the purpose of risk analysis should be more clearly defined and that intellectual property issues should be further clarified.

148. The JECFA Secretariat recalled that procedures existed to ensure confidentiality of proprietary information in JECFA but that toxicological information was published in the report of the risk assessment.

149. The Committee agreed that a risk assessment policy should be established and the issue of "drugs with a long history of use" should be addressed, and noted that this was related to the establishment of lists of substances of interest to member governments that would be considered in the discussion on priorities (see also Agenda Item 12).

150. Regarding the provisions on the risk profile in paragraph 16, the JECFA Secretariat clarified that the qualitative risk profile should be provided by the delegation that initially proposed the substance for evaluation, in reply to the questionnaire sent to request comments on priorities.

Monitoring and review of the decisions taken

151. The Committee agreed that a list of veterinary drugs for which no ADI or MRL had been established should be compiled and discussed whether a policy should be established concerning the status of that list but did not come to a conclusion. Some delegations pointed out that the absence of a MRL did not directly relate to a food safety issue, as in some cases MRLs had not been established, due to insufficient data or lack of data for minor species. In reply to a question, the JECFA Secretariat indicated that a Summary of JECFA Evaluations of Veterinary Drugs Residues from the 32nd Meeting to the present (62nd Meeting) had been published in the document FAO FNP 41/16. This document also contains a list of compounds which have been evaluated by JECFA but for which an ADI and/or MRL was not recommended.

152. The Committee recalled the request of the Commission for Codex Committees to complete their work on guidelines on risk analysis in their respective areas and agreed that the discussion paper should be redrafted as a working document for inclusion in the Procedural Manual, with a view to its

finalization at the next session. The Committee agreed that the document was being developed in response to a direct request of the Commission and did not need to go through the Step Procedure.

153. The Committee agreed that the document should be redrafted by the Delegation of France with the assistance of a working group[15] taking into account the written comments, the discussion at the present session, and the recommendations of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, where applicable. It requested the Working Group to submit the revised version by September 2005, for comments and consideration by the next session.

16th Session of CCRVDF (May 2006) (ALINORM 06/29/31, para. 111 and Appendices VII and IX)

At its 16th Session, the Committee considered the revised paper on risk management methodologies (CX/RVDF 06/16/10) which included two texts on: Risk Analysis Methodologies in the Codex Committee on Residues of Veterinary Drugs in Foods and Risk Assessment Policy for the Setting of MRLs in Food.

111. The Committee agreed to forward the renamed Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and the Risk Assessment Policy for the Setting of MRLs in Food to the Codex Alimentarius Commission, through the Codex Committee on General Principles, for adoption and inclusion in the Codex Procedural Manual (see Appendices VIII and IX).

ALINORM 06/29/31, Appendix VIII

PROPOSED DRAFT
RISK ANALYSIS PRINCIPLES APPLIED BY THE CODEX COMMITTEE
ON RESIDUES OF VETERINARY DRUGS IN FOODS
(for inclusion in the Codex Procedural Manual)

1. PURPOSE – SCOPE

1. The purpose of this document is to specify Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods.

2. PARTIES INVOLVED

2. The *Working Principles for Risk Analysis for application in the framework of the Codex Alimentarius*[16] has defined the responsibilities of the various parties involved. The responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission (CAC) and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRDVF), while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3. According to its mandate, the responsibilities of CCRVDF regarding veterinary drug residues in food are:

[15] Australia, Burkina Faso, Brazil, Canada, China, Colombia, Costa Rica, European Community, Japan, Korea, Malaysia, Netherlands, Switzerland, Sweden, Thailand, United States, ALA, CI, IFAH, OIE, and OIRSA

[16] Codex Procedural Manual, 15th Edition page 101 (English version).

(a) to determine priorities for the consideration of residues of veterinary drugs in foods;

(b) to recommend MRLs for such veterinary drugs;

(c) to develop codes of practice as may be required;

(d) to consider whether available methods of sampling and analysis for the determination of veterinary drug residues in foods.

4. CCRVDF shall base its risk management recommendations to the Codex Alimentarius Commission (CAC) on JECFA's risk assessments of veterinary drugs in relation to proposed MRLs.

5. CCRVDF is primarily responsible for recommending risk management proposals for adoption by the Codex Alimentarius Commission (CAC).

6. JECFA is primarily responsible for providing independent scientific advice, the risk assessment, upon which CCRVDF base their risk management decisions. It assists the CCRVDF by evaluating the available scientific data on the veterinary drug prioritised by CCRVDF. JECFA also provides advice directly to FAO and WHO and to Member governments.

7. Scientific experts from JECFA are selected in a transparent manner by FAO and WHO under their rules for expert committees on the basis of the competence, expertise, experience in the evaluation of compounds used as veterinary drugs and their independence with regard to the interests involved, taking into account geographical representation where possible.

3. RISK MANAGEMENT IN CCRVDF

8. Risk management should follow a structured approach including:

– preliminary risk management activities;

– evaluation of risk management options; and

– monitoring and review of decisions taken.

9. The decisions should be based on risk assessment, and take into account, where appropriate, other legitimate factors relevant for the health protection of consumers and for fair practices in food trade, in accordance with the *Criteria for the Consideration of the Other Factors Referred to in the Second Statement of Principles*[17].

3.1 PRELIMINARY RISK MANAGEMENT ACTIVITIES

10. This first phase of risk management covers:

– Establishment of risk assessment policy for the conduct of the risk assessments;

– Identification of a food safety problem;

– Establishment of a preliminary risk profile;

– Ranking of the hazard for risk assessment and risk management priority;

[17] Codex Procedural Manual, 15th Edition page 159 (English version)

– Commissioning of the risk assessment; and

– Consideration of the result of the risk assessment.

3.1.1 Risk Assessment Policy for the Conduct of the Risk Assessment

11. The responsibilities of CCRVDF and JECFA and their interactions along with core principles and expectations of JECFA evaluations are provided in *Risk Assessment Policy for the Setting of MRLs in Food*, established by the Codex alimentarius Commission.

3.1.2 Identification of a Food Safety Problem (establishment of the priority list)

12. CCRVDF identifies, with the assistance of Members, the veterinary drugs that may pose a consumer safety problem and/or have a potential adverse impact on international trade. CCRVDF establishes a priority list for assessment by JECFA.

13. In order to appear on the priority list of veterinary drugs for the establishment of a maximum residue limit (MRL), the proposed veterinary drug shall meet some or all of the following criteria:

– A Member has proposed the compound for evaluation;

– A Member has established good veterinary practices with regard to the compound;

– The compound has the potential to cause public health and/or international trade problems;

– It is available as a commercial product; and

– There is a commitment that a dossier will be made available.

14. The CCRVDF takes into account the protection of confidential information in accordance with WTO rules article 39, and makes every effort to encourage the willingness of sponsors to provide data for JECFA assessment.

3.1.3 Establishment of a Preliminary Risk Profile

15. Member(s) request(s) the inclusion of a veterinary drug on the priority list. The available information for evaluating the request shall be provided either directly by the Member(s) or by the sponsor. A preliminary risk profile shall be developed by the Member(s) making the request, using the template presented in the ANNEX.

16. The CCRVDF considers the preliminary risk profile and makes a decision on whether or not to include the veterinary drug in the priority list.

3.1.4 Ranking of the Hazard for Risk Assessment and Risk Management Priority

17. The CCRVDF establishes an ad-hoc Working Group open to all its Members and observers, to make recommendations on the veterinary drugs to include into (or to remove from) the priority list of veterinary drugs for the JECFA assessment. The CCRVDF considers these recommendations before agreeing on the priority list. taking into account pending issues such as temporary Acceptable Daily Intakes (ADIs) and/or MRLs. In its report, the CCRVDF shall specify the reasons for its choice and the criteria used to establish the order of priority.

18. Prior to development of MRLs for new veterinary drugs not previously evaluated by JECFA, a proposal for this work shall be sent to the Codex Alimentarius Commission with a request for approval as new work in accordance with the Procedures for the Elaboration of Codex Standards and Related Texts.[18]

3.1.5 Commissioning of the Risk Assessment

19. After approval by the Codex Alimentarius Commission of the priority list of veterinary drugs as new work, the CCRVDF forwards it to the JECFA with the qualitative preliminary risk profile as well as specific guidance on the CCRVDF risk assessment request. JECFA, WHO and FAO experts then proceed with the assessment of risks related to these veterinary drugs, based on the dossier provided and/or all other available scientific information.

3.1.6 Consideration of the Result of the Risk Assessment

20. When the JECFA risk assessment is completed, a detailed report is prepared for the subsequent session of the CCRVDF for consideration. This report shall clearly indicate the choices made during the risk assessment with respect to scientific uncertainties and the level of confidence in the studies provided.

21. When the data are insufficient, JECFA may recommend temporary MRL on the basis of a temporary ADI using additional safety considerations[19]. If JECFA cannot propose an ADI and/or MRLs due to lack of data, its report should clearly indicate the gaps and a timeframe in which data should be submitted, in order to allow Members to make an appropriate risk management decision.

22. The JECFA assessment reports related to the concerned veterinary drugs should be made available in sufficient time prior to a CCRVDF meeting to allow for careful consideration by Members. If this is, in exceptional cases not possible, a provisional report should be made available.

23. The JECFA should, if necessary, propose different risk management options. In consequence, JECFA should present, in its report, different risk management options for CCRVDF to consider. The reporting format should clearly distinguish between the risk assessment and the evaluation of the risk management options.

24. The CCRVDF may ask JECFA any additional explanation.

25. Reasons, discussions and conclusions (or the absence thereof) on risk assessment should be clearly documented, in JECFA reports, for each option reviewed. The risk management decision taken by CCRVDF (or the absence thereof) should also be fully documented.

3.2 EVALUATION OF RISK MANAGEMENT OPTIONS

26. The CCRVDF shall proceed with a critical evaluation of the JECFA proposals on MRLs and may consider other legitimate factors relevant for health protection and fair trade practices in the framework of the risk analysis. According to the 2nd statement of principle, the criteria for the consideration of other factors should be taken into account. These other legitimate factors are those agreed during the 12th session of the CCRVDF[20] and subsequent amendments made by this Committee.

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[18] Codex Procedural Manual, 15th Edition pages 19-30 (English version).
[19] Codex Procedural Manual, 15th Edition page 45 (English version).
[20] See Report of the 12th session of the CCRVDF ALINORM 01/31 para 11.

27. The CCRVDF either recommends the MRLs as proposed by JECFA, modifies them in consideration of other legitimate factors, considers other measures or asks JECFA for reconsideration of the residue evaluation for the veterinary drug in question.

28. Particular attention should be given to availability of analytical methods used for residue detection.

3.3 MONITORING AND REVIEW OF THE DECISIONS TAKEN

29. Members may ask for the review of decisions taken by the Codex Alimentarius Commission. To this end, veterinary drugs should be proposed for inclusion in the priority list. In particular, review of decisions may be necessary if they pose difficulties in the application of the *Guidelines for the Establishment of a Regulatory Program for the Control of Veterinary Drug Residues in Foods.*

30. CCRVDF may request JECFA to review any new scientific knowledge and other information relevant to risk assessment and concerning decisions already taken, including the established MRLs.

31. The risk assessment policy for MRL shall be reconsidered based on new issues and experience with the risk analysis of veterinary drugs. To this end, interaction with JECFA is essential. A review may be undertaken of the veterinary drugs appearing on prior JECFA agendas for which no ADI or MRL has been recommended.

4. RISK COMMUNICATION IN THE CONTEXT OF RISK MANAGEMENT

32. In accordance with the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius*[21], the CCRVDF, in cooperation with JECFA, shall ensure that the risk analysis process is fully transparent and thoroughly documented and that results are made available in a timely manner to Members. The CCRVDF recognises that communication between risk assessors and risk managers is critical to the success of risk analysis activities.

33. In order to ensure the transparency of the assessment process in JECFA, the CCRVDF provides comments on the guidelines related to assessment procedures being drafted or published by JECFA.

ANNEX

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CCRVDF

Administrative information

1. Member(s) submitting the request for inclusion

2. Veterinary drug names

3. Trade names

4. Chemical names

5. Names and addresses of basic producers

[21] Codex Procedural Manual, 15th Edition page 161 (English version).

Purpose, scope and rationale

6. Identification of the food safety issue (residue hazard)

7. Assessment against the criteria for the inclusion on the priority list

Risk profile elements

8. Justification for use

9. Veterinary use pattern

10. Commodities for which Codex MRLs are required

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework

12. Specific request to risk assessors

Available information[22]

13. Countries where the veterinary drugs is registered

14. National/Regional MRLs or any other applicable tolerances

15. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

Timetable

16. Date when data could be submitted to JECFA

ALINORM 06/29/31, Appendix IX

PROPOSED DRAFT
RISK ASSESSMENT POLICY FOR THE SETTING OF MRLS IN FOOD
(for inclusion in the Codex Procedural Manual)

ROLE OF JECFA

1. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an independent scientific expert body convened by both Director Generals of FAO and WHO according to the rules

[22] When preparing a preliminary risk profile, Member(s) should take into account the updated data requirement, to enable evaluation of a veterinary drug for the establishment of an ADI and MRLs, published by JECFA.

of both organizations, charged with the task to provide scientific advice on veterinary drug residues in food.

2. This annex applies to the work of JECFA in the context of Codex and in particular as it relates to advice requests from CCRVDF

(a) JECFA provides CCRVDF with science-based risk assessments conducted in accordance with the *Statements of principles relating to the role of food safety risk assessment*[23] and incorporating the four steps of risk assessment. JECFA should continue to use its risk assessment process for establishing ADIs and proposing MRLs.

(b) JECFA should take into account all available scientific data to establish its risk assessment. It should use available quantitative information to the greatest extent possible and also qualitative information.

(c) Constraints, uncertainties and assumptions that have an impact on the risk assessment need be clearly communicated by JECFA.

(d) JECFA should provide CCRVDF with information on the applicability, public health consequences and any constraints of the risk assessment to the general population and to particular sub-populations and, as far as possible, should identify potential risks to specific group of populations of potentially enhanced vulnerability (e.g. children).

(e) Risk assessment should be based on realistic exposure scenarios.

(f) When the veterinary drug is used both in veterinary medicine and as a pesticide, a harmonised approach between JECFA and JMPR should be followed.

(g) MRLs, that are compatible with the ADI, should be set for all species based on appropriate consumption figures. When requested by CCRVDF, extension of MRLs between species will be considered if appropriate data are available.

DATA PROTECTION

3. Considering the importance of intellectual property in the context of data submission for scientific evaluation, JECFA has established procedures to cover the confidentiality of certain data submitted. These procedures enable the sponsor to declare which data is to be considered as confidential. The procedure includes a formal consultation with the sponsor.

EXPRESSION OF RISK ASSESSMENT RESULTS IN TERMS OF MRLS

4. MRLs have to be established for target animal tissues (e.g. muscle, fat, or fat and skin, kidney, liver), and specific food commodities (e.g. eggs, milk, honey) originating from the target animals species to which a veterinary drug can be administered according to good veterinary practice.

5. However, if residue levels in various target tissues are very different, JECFA is requested to consider MRLs for a minimum of two. In this case, the establishment of MRLs for muscle or fat is preferred to enable the control of the safety of carcasses moving in international trade.

[23] Codex Procedural Manual 15th Edition page 161 (English version).

6. When the calculation of MRLs to be compatible with the ADI may be associated with a lengthy withdrawal period, JECFA should clearly describe the situation in its report.

ANNEX 8

DEFINITIONS OF RISK ANALYSIS TERMS RELATED TO FOOD SAFETY[24]

Hazard: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

Risk Analysis: A process consisting of three components: risk assessment, risk management and risk communication.

Risk Assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.

Risk Management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

Risk Assessment Policy: Documented guidelines on the choice of options and associated judgements for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained.

Risk Profile: The description of the food safety problem and its context.

Risk Characterization: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Risk Estimate: The quantitative estimation of risk resulting from risk characterization.

Hazard Identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

Hazard Characterization: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.

Dose-Response Assessment: The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response).

[24] Procedural Manual of the Codex Alimentarius Commission (15th Edition).

Exposure Assessment: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.

Food Safety Objective (FSO): The maximum frequency and/or concentration of a hazard in a food at the time of consumption that provides or contributes to the appropriate level of protection (ALOP).

Performance Criterion (PC): The effect in frequency and/or concentration of a hazard in a food that must be achieved by the application of one or more control measures to provide or contribute to a PO or an FSO.

Performance Objective (PO): The maximum frequency and/or concentration of a hazard in a food at a specified step in the food chain before the time of consumption that provides or contributes to an FSO or ALOP, as applicable.

ANNEX 9

RECOMMENDED INTERNATIONAL CODE OF PRACTICE FOR CONTROL OF THE USE OF VETERINARY DRUGS

CAC/RCP 38-1993

INTRODUCTION

1. This Code sets out guidelines on the prescription, application, distribution and control of drugs used for treating animals, preserving animal health or improving animal production. The Code is intended to apply to all States which are members of the organizations under whose auspices the project is being developed and to contribute towards the protection of public health.

2. Good practice in the use of veterinary drugs (GPVD), as defined by the CCRVDF, is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions. The maximum residue limit for veterinary drugs (MRLVD) may be reduced to be consistent with good practice in the use of veterinary drugs. The MRLVD is based on the type and amount of residue considered to be without toxicological hazard for human health while taking into account other relevant public health risks as well as food technological aspects.

3. Veterinary products (including premixes for manufacture of medicated feedingstuffs) used in food producing animals should be administered (or incorporated into feed) in compliance with the relevant product information approved by national authorities and/or in accordance with a prescription and/or instruction issued by a qualified veterinarian.

REGISTRATION AND DISTRIBUTION - GENERAL REQUIREMENTS

4. All medicinal products (i.e., all veterinary therapeutic products) and medicinal premixes for inclusion in animal feeds should comply with the OIE Code of Practice for the Registration of Veterinary Drugs and be registered with the national authority. Products should only be distributed through veterinarians, registered wholesalers, pharmacists or other retail outlets permitted by national laws and regulations. Records of products taken into and leaving the premises should be maintained. Storage and transport conditions must conform to the specifications on the label, in particular those concerning temperature, humidity, light, etc.

RESPONSIBILITY OF THE VETERINARIAN AND OF OTHERS AUTHORIZED TO HANDLE OR ADMINISTER MEDICINES - GENERAL PROVISIONS

5. Whenever veterinary drugs are handled or administered it is important to recognize that potentially hazardous effects may occur in animals or in human operators. When the administration of a medicine is not under direct veterinary supervision, it is therefore essential that, after the diagnosis, clear instructions should be provided on dose and methods of use, taking account of the competence of the user performing the work and ensuring that the correct calculation of, and the importance of adhering to, withdrawal periods is fully understood. It is similarly important to ensure that the farm facilities and management systems employed enable the withdrawal periods to be observed.

6. In determining treatments, it is necessary to ensure that an accurate diagnosis is obtained and be guided by the principles of maximum effectiveness combined with minimum risk. Specific

treatments should be presented using as few products as possible and avoiding the use of combination products, unless pharmacological advantages have been demonstrated.

7. Veterinarians should keep in mind that uncontrolled and unlimited use of medicinal products may lead to the accumulation of undesirable residues in the animals treated and in the environment, and that the continuous use of anticoccidial, antibacterial or anthelmintic products may favour the development of resistance. It is the responsibility of the veterinarian or other authorized persons to draw up programmes of preventive medicine for the farmer and to stress the importance of sound management and good husbandry procedures in order to reduce the likelihood of animal diseases. Every effort should be made to use only those drugs known to be effective in treating the specific disease.

8. The veterinarian should stress the need for diseased animals to be segregated from healthy animals and treated individually where possible.

9. Beyond his responsibility for advice on measures that will reduce the incidence of disease and for controlling it when it arises, the veterinarian is also responsible for taking the welfare of livestock fully into account.

INFORMATION OF VETERINARY DRUGS

10. Product information considered essential by the national authority to ensure the safe and effective use of veterinary medicinal products must be made available in the form of labelling, data sheets or leaflets. Information on dosage schedules should be complemented by instructions on dose-related recommended withdrawal periods, interactions, contra-indications and any other constraints on the use of the product including any precautions regarded as necessary.

AMOUNTS TO BE SUPPLIED

11. Medicines should not be supplied in excess of immediate requirements as this may lead to incorrect use or to deterioration of the products.

PREPARATION OF MEDICINES

12. The preparation of medicines and medicated feeds should be undertaken by suitably trained personnel, using appropriate techniques and equipment.

ADMINISTRATION OF MEDICINES

13. Special attention should be paid to the prescription and to using the correct dosage, site and route of administration. Note should be taken of all warning statements, interactions and contra-indications for use (in particular any incompatibility with other medicinal products). It is important not to use the product once the expiry date has passed.

14. In disease circumstances where no authorized product exists or certain indications or target species are not provided for in the product literature, the veterinarian can on his own responsibility or with advice from the manufacturer have recourse to other licensed products or off label use. Administration of products in this manner, however, may have unpredictable side effects and give rise to unacceptable residue levels. Veterinarians should therefore only embark on such uses, especially in food-producing animals, after the most careful consideration of the needs of the disease situation. Under these circumstances, a significantly extended withdrawal time should be assigned for drug withdrawal prior to marketing milk, meat or eggs. The veterinarian is responsible for providing written instructions on the use and withdrawal times for all medicines used off label. Off label use by

persons other than veterinarians must not be permitted except when such use is conducted or permitted under the supervision or prescription of the veterinarian.

15. To avoid the presence of unacceptable residues in meat or other by-products of animal origin, it is essential that the livestock owner adheres to the withdrawal period laid down for each product and dose regime or to a suitably lengthy withdrawal period, prescribed by a veterinarian, where none is specified. Full instructions should be given as to how this period is to be observed, including the use of on site residue detection methods where applicable and on the disposal of any animals slaughtered during treatment or before the end of the withdrawal period. If animals are sold before the end of the withdrawal period, the buyer must be informed.

RECORD KEEPING REQUIREMENTS

16. The veterinarian and/or the livestock owner or other authorized persons should keep a record of the products used, including the quantity, the date of administration and the identity of animals on which the medicines were used. Each record should be kept for at least two years, and presented when required by the competent authorities.

WITHDRAWAL OF VETERINARY DRUGS

17. Where the veterinarian or other authorized person suspects that unexpected adverse reactions involving illness, abnormal clinical signs, or death in animals, or any harmful effects in persons administering veterinary medicines have been associated with a veterinary product, they should be reported to the appropriate national authority. Regular feed-back or information to veterinarians and manufacturers on suspected adverse reactions should be encouraged.

STORAGE OF VETERINARY DRUGS

18. Veterinary products should be correctly stored in accordance with label instructions. It should be kept in mind that storage temperatures are critical for some medicines, while exposure to light or to moisture can damage others. Prescription medicines should be separated from non-prescription medicines.

19. All veterinary products should be stored in secure premises and kept under lock and key where practicable and out of reach of children and animals.

DISPOSAL OF VETERINARY DRUGS

20. Veterinary drugs remaining after treatment has been completed must be disposed of safely according to labelled instructions. Partially used containers should not be retained for future use. Unused drugs beyond their expiry date may however be returned to the vendor if there is an agreement to that effect. Where administration of medicines is not under direct veterinary supervision, users should be advised about correct disposal measures, e.g., to reduce potential contamination of the environment.

DISPOSAL AND CLEANING OF DRUG ADMINISTRATION EQUIPMENT

21. Disposable equipment used for administration of veterinary drugs must be disposed of safely and in accordance with correct disposal procedures. Where drugs are not administered under veterinary supervision, disposable syringes, needles, catheters and other drug administration equipment should, wherever practicable, be returned to the supplying veterinary practice to ensure correct disposal procedures.

22. Cleaning of equipment used for the administration of veterinary drugs must be carried out in a manner that ensures the safety of human health and the environment. After cleaning, any material containing residues of the veterinary drug should be disposed of using the same procedures that apply to disposal of the drug itself.

ANNEX 10

CODEX GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAMME FOR CONTROL OF VETERINARY DRUG RESIDUES IN FOODS

CAC/GL 16-1993

Governments need regulatory control programmes to ensure their citizens of a safe and wholesome food supply. Specifications of a residue control programme are determined by the importance of the various health risks that could be incurred by consumers of products derived from animal food products.

One type of risk may occur if meat is handled and consumed from animals excessively contaminated with microorganisms or toxins that could affect the health of consumers. This type of health risk can be minimized by establishing meat inspection programmes that emphasize appropriate and provide specific procedures on how to recognize the signs of disease in food producing animals.

Another kind of risk can occur if food animals have been raised using veterinary drugs or pesticides in an inappropriate manner. The improper use of such chemicals can result in unsafe residues of these substances in food derived from the treated animals. The safety of the human food requires a full scientific evaluation of the relative hazard as well as quantity of a drug residue remaining in the tissues of treated livestock and poultry when used according to good veterinary practices, and a systematic set of procedures that will ensure effective control of such residues in human food.

In addition to the health protection benefits in having an effective residue control programme, a country with such a programme has the capability to participate in the community of food trading nations with greater confidence. This is because an effective residue control programme can also serve as the foundation for certifying the safety of the country's exported food products, as well as provide assurance of safety of such products imported into the country.

When establishing a programme for control of residues in foods, it is important to distinguish between the notion of "unbiased statistical sampling", where the samples are obtained from animals that are presented for inspection, and the notion of "biased or directed sampling", where samples are obtained from suspect food products. The purpose of unbiased statistical sampling is to determine the frequency of occurrence of contaminated products among those presented for inspection.

Samples are taken at random from food considered safe, and it is not necessary to retain these food products while waiting for the results of analytical testing. The sampling plan is determined beforehand, using statistical rules to ensure that the results are representative of the overall quality of the product(s) under consideration. The results may be used to certify the exported food products are in compliance with Codex MRLVDs. Conversely, directed sampling focuses on food products suspected of having residue concentrations that exceed the maximum residue limits. The food products are detained while waiting for results of laboratory testing, and are not released for human consumption should test results be unfavourable. The number of samples to be taken during the year for directed sampling may not, by definition, be predetermined. The results of directed sampling do not have statistical representativeness.

In establishing an effective residue control programme, a country should first establish a comprehensive system for determining the safety of veterinary drugs. This may be accomplished, for example, through an organization with suitable technical expertise and administrative authority. Veterinary drugs may be approved taking into consideration several relevant criteria, among which

will be the safety evaluation of the veterinary drug for animals and for human food consumption. The scientific evaluation of the safety of veterinary drugs is a long and rigorous task, that, perhaps, may not be necessary to perform in each country, especially in developing countries. Evaluation could be performed by the interested country, using the technical expertise of international organizations such as the Joint FAO/WHO Expert Committee on Food Additives (for veterinary drugs), or the technical evaluation results in other countries having an acceptable, technically qualified safety assessment organizations.

To establish an effective programme for the control of residues of veterinary drugs in food, a country should include but not necessarily be limited to the following items:

1. Establishing the regulatory authority responsibility for implementing inspection programmes and laboratory analyses.

2. Elaborating an integrated inspection programme, including a residue control programme for the inspection of foods. The organization in charge of implementing this inspection programme should be granted the authority to take all the steps necessary to control products when residues exceed the maximum residue limits established for a food commodity.

3. Compiling a register of veterinary drugs and/or pure chemical; substances used in the country, including the products manufactured in the country and those products that are imported into the country.

4. Elaborating regulations concerning the distribution of veterinary drugs as a whole, providing for procedures for the authorized sale, manufacture, distribution and use of such products.

5. Elaborating procedures for determining the safety and efficacy of veterinary drugs in animals and residues in food from use of such veterinary drugs. This should include describing procedures for determining maximum residue limits for veterinary drugs in food and procedures for analysis of test samples intended to verify compliance with those limits.

6. Establishing procedures for sampling food products of animal origin, indicating the specific drug residues of greatest health concern, the number of samples to be taken for unbiased statistical sampling, and the nature of the tissue and quantity of sample to be taken. Procedures for sampling for residue control in a country may be required for certain substances for purposes other than the enforcement of MRLVDs. These analyses, for example, come within the scope of exploratory surveys for determining residues in foods where unapproved substances may be used in food producing animals or poultry. This type of data is essential to provide a residue control programme the flexibility necessary to be adapted to national needs.

7. Selecting the methods of analysis to be used. As an initial step, a residue control programme should include screening methods. The use of these methods should not require investment in complex laboratory instrumentation nor in costly reagents or personnel training, and should provide analysis of samples in a cost effective manner. Screening methods are generally defined as qualitative or semi-quantitative methods of analysis that detect the presence of a substance at a concentration that is equal to or lower than the maximum residue limits. A positive result indicates the possibility that the maximum residue limit has been exceeded. Additional testing measures should be required, as determined by the objectives set forth in a country's residue control programme, to verify or confirm the results of screening methods.

8. Implementing a quality assurance programme to assure the highest quality results for methods of analysis. Such a programme will assure regulatory control authorities that the methods used will

give reliable results that are compatible with the MRLVD or within the limits established by national regulations.

9. Developing an educational programme(s) for producers and veterinarians providing instruction in the proper use of veterinary drugs, and encouraging the use of preventive measure to reduce the occurrence of residues in food animals and poultry.

For determining maximum residue limits, the Joint FAO/WHO Expert Committee on Food Additives (for veterinary drugs) may constitute a useful resource for obtaining these data.

10. Specific details concerning the establishment of a regulatory programme for control of veterinary drug residues in foods, as based on the above general principles, are attached to these guidelines as follows:

PART 1:	Sampling for the Control of Residues of Veterinary Drugs in Foods
Appendix A:	Sampling for the Control of Veterinary Drug Residues in Meat and Poultry Products
Appendix B:	Sampling for the Control of Veterinary Drug Residues in Fish, Milk, and Egg Products
Appendix C:	Sampling for the Control of Veterinary Drug Residues in Honey
PART 2:	General Considerations on Analytical Methods for Residue Control
PART 3:	Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods

PART I

SAMPLING FOR THE CONTROL OF RESIDUES OF VETERINARY DRUGS IN FOODS

1. INTRODUCTION

1.1 Basis for the Sampling Principle

The Codex Alimentarius Commission has decided that recommended sampling procedures for food additives, pesticide residues and residues of veterinary drugs in food are exempted from the general sampling procedures of food commodities developed by the Codex Committee on Methods of Analysis and Sampling - Normal Practice. That committee's work is concerned mainly with sampling procedures for the visible and measurable qualities and attributes of various commodities and foods; sampling to determine whether standards of identity and composition have been met and to measure traditional attributes of quality, such as dust and moisture content in grain. The Codex Committees that are responsible for establishing permitted levels of regulated added substances - food additives, pesticides, veterinary drugs in food, have been given authority to prepare their own recommendations for methods of analysis and sampling. In this regard, the Codex Committee on Residues of Veterinary Drugs in Foods established an *Ad Hoc* Working Group on Methods of Analysis and Sampling at its first meeting.

1.2 General Principles

Sampling for analytical testing is only one element of a country's residue control programme and, by itself, cannot accomplish the entire objective of protecting public health. Sampling is a tool used as part of the system for developing information to determine if a supply of foodstuffs meets public health requirements, in this case, that the concentration of veterinary drug residues are within specified limits.

Sampling has varying purposes and statistical parameters. This guideline discusses the various objectives which sampling may address and provides technical guidance to be applied for sampling products within the terms of reference of this Codex Committee. By using Codex standards, including agreed upon sampling methods, member countries can comply with Article III of the General Agreement on Tariffs and Trade.

In sampling for residues of an added, regulated substance such as a veterinary drug, it is important to sample as near as possible to where animals raised for food are cared for and slaughtered in herds or flocks. The most meaningful sampling for tissue residues will occur in conjunction with slaughter. For other food products within the scope of this Committee, such as honey, the most meaningful sampling for residues will occur at the time of collection, prior to commingling of samples from different producers.

Sampling at an abattoir in conjunction with slaughter of a herd or flock or with preliminary slaughter of a small number of test animals or birds, may involve testing samples drawn from live animals or birds. In these situations, analyses performed on tissues drawn from test animals or body fluids from live animals may provide test results for an inspector before a herd or flock is presented for slaughter or shipment. Analyses associated with pre-slaughter must be designed to prevent subsequent administration of drugs. In a like manner, for processed foods such as might be obtained from fish or honey, any sampling and testing must be designed to prevent subsequent administration of drugs. When body fluids are used for residue testing, care must be taken to have established tissue-fluid relationships between the analytic results in these fluids and results in tissues where the MRLVDs are established.

Shortly after slaughter or after appropriately harvesting the principle food products, these products may be commingled to an extent that it destroys the possibility of drawing a representative sample. Samples for fresh meat or poultry or fresh chilled meat or poultry may be drawn from different days' production, for example. Processed products such as sausage or minced fish may be made with meat tissues from different days' or even different establishments' production. Although under some circumstances lots for sampling have been defined as products from the same consignor or packer, sample homogeneity can best be guaranteed when it is taken in conjunction with slaughter or primary collection point.

2. OBJECTIVES OF SAMPLING

2.1 Primary Point of Origin Sampling

2.1.1 Non-biased sampling

Non-biased sampling is designed to provide profile information on the occurrence of residues in specified food producing populations on an annual, national basis. For residue testing, the focus is on gathering information on the prevalence of residue violations; therefore, only compounds with established safe limits such as MRLVDs are usually considered for residue testing programmes. Compounds selected for statistically designed non-biased sampling are usually based on risk profiles (considering toxicity of residues and use) and the availability of laboratory methods suitable for regulatory control purposes. Information is obtained through a statistically based selection of random samples from animals presented for inspection. Limited or geographical area sampling may be conducted where a localized potential drug residue problem appears. The information obtained from this type of sampling should be reviewed periodically to assess residue control programmes and to allocate resources according to specific needs.

In addition to profile information, residue data provides a basis for further regulatory action. In particular, the results can be used to identify producers marketing animals, or other food commodity within the terms of reference of this Committee, with violative concentrations of residues. When these producers subsequently bring animals, fish or honey for inspection, they will be subjected to more directed and specific sampling and testing until compliance with MRLVDs is demonstrated. Other auxiliary uses of the data are to indicate prevalence and concentrations of residue violations, to evaluate residue trends, and to identify residue problem areas within the industry where educational or other corrective efforts may be needed. Thus, non-biased sampling gathers information and assists in deterring practices that lead to residue violations.

As a general practice, samples collected by inspectors are sent for residue analysis to a laboratory designated by national authorities. Now, however, advances in analytical technology provide inspection authorities an opportunity for performing residue screening tests on commodities at an abattoir or similar facility. In these situations, inspectors may send tissue samples to a laboratory designated by national authorities for more definitive analyses when results obtained from the screening test suggest a positive residue finding.

In some cases and situations where samples are sent directly to a designated laboratory for residue testing, the laboratory results may not be available until after the product has moved into consumer markets and become untraceable. Because of this pragmatic limitation, some animals, fish or honey containing violative residues may inevitably pass into consumer markets, regardless of the regulatory control efforts to limit this occurrence as much as possible. The consequences to human health, however, are minimal as long as the frequency of violative residues is low. This is because MRLVDs represent the maximum residue concentration determined to be safe for daily consumption within the limits of the acceptable daily intake (ADI) over a lifetime. As a result of employing safety

factors for determining an ADI, and subsequently the MRLVD, the occasional consumption of products with slightly higher residue concentrations than the MRLVD is unlikely to result in adverse health effects.

Non-biased sampling should have a statistically specified reliability. This may be expressed in reference to a confidence level and a prevalence rate. For example, sampling may be designed to detect, with 95% certainty, a prevalence occurring in 1% of healthy animals submitted for inspection. When a confidence level and prevalence rate is established, the number of samples necessary to achieve the desired objective can be determined from Table 1.

Table 1: Number of samples required to detect at least one violation with predefined probabilities (i.e., 90, 95, and 99 percent) in a population having a known violation prevalence.

Violation prevalence (% in a population)	Minimum number of samples required to detect a violation with a confidence level of:		
	90%	95%	99%
35	6	7	11
30	7	9	13
25	9	11	17
20	11	14	21
15	15	19	29
10	22	29	44
5	45	59	90
1	230	299	459
0.5	460	598	919
0.1	2302	2995	4603

2.1.2 Directed sampling

Directed sampling is designed to investigate and control the movement of potentially adulterated products. The sampling is often purposely biased and is directed at particular carcasses, products or producers in response to information from statistically based sampling (or other regulatory control agency data), or from inspector observations during ante-mortem or post-mortem inspection indicating that violative residues may be present. In-plant or on site residue testing procedures may be performed by the inspector, or samples may be submitted for analysis to a laboratory designated by national authorities. Depending upon the weight of evidence for testing in support of directed sampling, product may be retained until test results indicate the appropriate regulatory disposition. Laboratory analysis of directed residue test samples should be completed as rapidly as possible and take precedence over routine, statistically based samples. In directed sampling situations, herds of animals, flocks of birds, lots of fish or honey, should be considered unacceptable until it can be demonstrated that they are in compliance with Codex MRLVDs or national regulations in the country of origin for the specific commodity.

The probability of failing to detect a residue violation and accepting the lot depends upon the directed sampling programmes' sample size and prevalence of the residue violation frequency. Table 2 shows the probability of failing to detect a residue violation using different sample sizes from an "infinite" population with a specified proportion of violations. For example, selecting 5 samples from a large lot in which 10 percent of the units contain violative residues would, on the average, fail to detect a residue violation in 59.0 percent of such lots (i.e., 59.0 percent of the lots would be

accepted). Assuming the same conditions as the previous example, but using a sample size of 50, would result in only 0.5 percent of such lots being accepted.

Table 2: Probability of failing to detect a residue violation

Prevalence	Number of animals in sample tested									
(%)	5	10	25	50	75	100	200	250	500	1000
1	0.951	0.904	0.779	0.605	0.471	0.366	0.134	0.081	0.007	0.000
2	0.904	0.817	0.603	0.364	0.220	0.133	0.018	0.006	0.000	
3	0.859	0.737	0.467	0.218	0.102	0.048	0.002	0.000		
4	0.815	0.665	0.360	0.130	0.047	0.017	0.000			
5	0.774	0.599	0.277	0.077	0.021	0.006				
6	0.734	0.539	0.213	0.045	0.010	0.002				
7	0.696	0.484	0.163	0.027	0.004	0.001				
8	0.659	0.434	0.124	0.015	0.002	0.000				
9	0.624	0.389	0.095	0.009	0.001					
10	0.590	0.349	0.072	0.005	0.000					
12	0.528	0.279	0.041	0.002						
14	0.470	0.221	0.023	0.001						
16	0.418	0.175	0.013	0.000						
18	0.371	0.137	0.007							
20	0.328	0.107	0.004							
24	0.254	0.064	0.001							
28	0.193	0.037	0.000							
32	0.145	0.021								
36	0.107	0.012								
40	0.078	0.006								
50	0.031	0.001								
60	0.010	0.000								

Risk and cost factors should be considered in determining the sample sizes used in a directed sampling programme. Also, because of possible gains in the probability of detecting unacceptable herds of animals, flocks of birds, lots of fish or honey due to residue violations, the feasibility of selecting separate samples from separate lots instead of from a single lot should be considered.

2.2 Secondary Point of Sampling

2.2.1 Port of entry sampling

Port of entry testing of products derived from food producing animals, poultry, or fish, and honey, imported by member countries of Codex Alimentarius is a means of verifying the effectiveness of the exporting country's residue control programme. The purpose of port of entry sampling and testing is not to replace an exporting country's residue control programmes.

Results of residue testing that indicate imported product is in compliance with Codex MRLVDs should be permitted to move into commerce. When test results indicate that imported product contains violative residues, subsequent shipments of the same product group from that

establishment or company should be retained at the port of entry until laboratory results indicating compliance with MRLVDs are known by regulatory control authorities. Consideration should be given to placing all subsequent shipments of similar products from the country of origin on an increased testing schedule until a record of compliance with Codex MRLVDs is re-established.

Compounds selected for residue testing at port of entry should take into account the compounds approved for use in the exporting country, as well as those included in the domestic residue control programme of the importing and exporting country. Guidance for collecting samples for port of entry testing is summarized in Appendix A, Table A, Appendix B, Table B and Appendix C.

Appendix A

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN MEAT AND POULTRY PRODUCTS

1. OBJECTIVE

To provide instructions for sampling a lot of meat or poultry products to determine compliance with Codex Maximum Residue Limits for Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 Lot

An identifiable quantity of food delivered for slaughter or distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official. Several lots may make up a consignment.

2.2 Consignment

A quantity of food as described on a particular contractor's shipping document. Lots in a consignment may have different origins or may be delivered at different times.

2.3 Primary Sample

A quantity of tissue taken from a single animal or from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one animal or location can be combined for the primary sample (such as poultry organs).

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The primary sample or a representative portion of the primary sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected Class B: Primary Food Commodities of Animal Origin

Type 06 Mammalian Products

No. 030 Mammalian Meat

No. 031 Mammalian Fats

No. 032 Mammalian Edible Offal

Type 07 Poultry Products

No. 036 Poultry Meats

No. 037 Poultry Fats

No. 038 Poultry Edible Offal

3.2 Selected Class E: Processed Products of Animal Origin made from only Primary Food Nos. 030, 032, 036, and 038

Type 16 - Secondary Products

Type 18 - Manufactured (single ingredient) Products of a Minimum of One Kilogram Container or Unit Size

Type 19 - Manufactured (multiple ingredient) Products of a Minimum of One Kilogram Container or Unit Size

4. PRINCIPLE ADOPTED

For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each laboratory sample taken from a lot. Lot compliance with a Codex MRLVD is achieved when none of the laboratory samples contains a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to Take

During collection and processing, contamination or other changes in the samples which would alter the residue or affect the analytical determination must be prevented.

6.3 Collection of a Primary Sample

Detailed instructions for collection of a primary sample of various products are provided in Table A. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Table A. The following are general instructions.

a. Each primary sample should be taken from a single animal or unit in a lot, and when possible, be selected randomly.

b. When multiple animals are required for adequate sample size of the primary sample (i.e., poultry organs), the samples should be collected consecutively after random selection of the starting point.

c. Canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. The primary sample should contain a representative portion of juices surrounding the product. Each sample should then be frozen as described in paragraph 6.8.d.

d. Frozen product should not be thawed before sampling.

e. Large, bone-containing units of product (i.e., prime cuts) should be sampled by collecting edible product only as the primary sample.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If a residue violation is suspected because of its origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport, by signs of toxicosis observed during ante- or post-mortem inspection, or by other relevant information available to the inspection official, the lot is designated a suspect lot. If there is no reason to suspect adulteration, the lot is designated a non-suspect lot.

6.4.1 Sampling suspect lots

A minimum of six to a maximum of thirty primary samples should be collected from a suspect lot. When the suspected adulteration is expected to occur throughout the lot or is readily identifiable within the lot, the smaller number of samples is sufficient.

6.4.2 Sampling non-suspect lots

A statistically-based, non-biased sampling programme is recommended for non-suspect lots. Any of the following types of sampling can be used.

a. Stratified random sampling

In a complex system where commodities must be sampled at many locations over extended time periods, it is very difficult to apply simple random criteria in the design of a sampling programme. A useful alternative sampling design is stratified random sampling which separates population elements into non-overlapping groups, called strata. Then samples are selected within each stratum by a simple random design. Homogeneity within each stratum is better than in the whole population. Countries or geographic regions are natural strata because of uniformity in agricultural practices. Time strata (e.g., month, quarter) are commonly used for convenience, efficiency, and detection of seasonal variability. Random number tables or other objective techniques

should be used to ensure that all elements of a population have an equal and independent chance of being included in the sample.

b. Systematic sampling

Systematic sampling is a method of selecting a sample from every 'K' quantity of product to be sampled, and then sampling every 'K' unit thereafter. Systematic sampling is quicker, easier, and less costly than non-biased sampling, when there is reliable information on product volumes to determine the sampling interval that will provide the desired number of samples over time. If the sampling system is too predictable, it may be abused. It is advisable to build some randomness around the sampling point within the sampling interval.

c. Biased or estimated worst case sampling

In biased or estimated worst case sampling, the investigator should use their judgement and experience regarding the population, lot, or sampling frame to decide which samples to select. As a non-random technique, no inferences should be made about the population sampled based on data collected. The population group anticipated to be at greatest risk may be identified.

Exporting countries should conduct a comprehensive residue testing programme and provide results to importing countries. Based on an importing country's data, testing may be conducted as applied to non-suspect products. Countries that do not provide residue testing results showing compliance with MRLVDs should be sampled as suspect lots.

6.5 Preparation of the Bulk Sample

The bulk sample is prepared by combining and thoroughly mixing the primary samples.

6.6 Preparation of the Final Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from it by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some national legislation may require the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Samples

a. Each sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.

b. The container should be sealed so that unauthorized opening is detectable.

c. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.

d. For shipping, all perishable samples should be frozen to minus 20^{o}C, immediately after collection, and packed in a suitable container that retards thawing. If possible,

the shipping container should be placed in a freezer for 24 hours prior to packing and shipping the frozen sample.

7. RECORDS

Each primary sample should be correctly identified by a record with the type of sample, its origin (e.g., country, state, or town), its location of collection, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

TABLE A: MEAT AND POULTRY PRODUCTS

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
I.	**Group 030** (Mammalian Meats)		
A.	Whole carcass or side, unit weight normally 10 kg or more	Collect diaphragm muscle, supplement with cervical muscle, if necessary, from one animal.	500 g
B.	Small carcass (e.g., rabbit)	Collect hind quarter or whole carcass from one or more animals.	500 g after removal of skin and bone
C.	Fresh/chilled parts		
	1. Unit minimum weight of 0.5 kg, excluding bone (e.g., quarters, shoulders, roasts)	Collect muscle from one unit.	500 g
	2. Unit weighing less than 0.5 kg (e.g., chops, fillets)	Collect the number of units from selected container to meet laboratory sample size requirements.	500 g after removal of bone
D.	Bulk frozen parts	Collect a frozen cross-section from selected container, or take muscle from one large part.	500 g
E.	Retail packaged frozen/chilled parts, or individually wrapped units for wholesale	For large cuts, collect muscle from one unit or take sample from number of units to meet laboratory sample size requirements.	500 g after removal of bone
Ia.	**Group 030** (Mammalian Meats where MRL is found in carcass fat)		
A.	Animals sampled at slaughter	See instructions under II. Group 031.	
B.	Other meat parts	Collect 500 g of visible fat, or sufficient product to yield 50-100 g of fat for analysis. (Normally 1.5-2.0 kg of product is required for cuts without trimmable fat).	Sufficient to yield 50-100 g of fat
II.	**Group 031** (Mammalian Fats)		
A.	Large animals sampled at slaughter, usually weighing at least 10 kg	Collect kidney, abdominal, or subcutaneous fat from one animal.	500 g

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
B.	Small animals sampled at slaughter[25]	Collect abdominal and subcutaneous fat from one or more animals.	500 g
C.	Bulk fat tissue	Collect equal size portions from 3 locations in container.	500 g
III.	**Group 032** (Mammalian Edible Offal)		
A.	Liver	Collect whole liver(s) or portion sufficient to meet laboratory sample size requirements.	400 - 500 g
B.	Kidney	Collect one or both kidneys, or kidneys from more than one animal, sufficient to meet laboratory sample size requirement. Do not collect from more than one animal if size meets the low range for sample size.	250 - 500 g
C.	Heart	Collect whole heart or ventricle portion sufficient to meet laboratory sample size requirement.	400 - 500 g
D.	Other fresh/chilled or frozen, edible offal product	Collect portion derived from one animal unless product from more than one animal is required to meet laboratory sample size requirement. A cross-section can be taken from bulk frozen product.	500 g
IV.	**Group 036** (Poultry Meats)		
A.	Whole carcass of large bird, typically weighing 2-3 kg or more (e.g., turkey, mature chicken, goose, duck)	Collect thigh, leg, and other dark meat from one bird.	500 g after removal of skin and bone
B.	Whole carcass of bird typically weighing between 0.5-2.0 kg (e.g., young chicken, duckling, guinea fowl)	Collect thigh, legs, and other dark meat from 3-6 birds, depending on size.	500 g after removal of skin and bone
C.	Whole carcasses of very small birds typically weighing less than 500 g (e.g., quail, pigeon)	Collect at least 6 whole carcasses.	250 - 500 g of muscle tissue
D.	Fresh/chilled or frozen parts 1. Wholesale packaged a. Large parts b. Small parts	Collect an interior unit from a selected container. Collect sufficient parts from a selected layer in the container.	500 g after removal of skin and bone
	2. Retail packaged	Collect a number of units from selected container to meet laboratory sample size requirement.	500 g after removal of skin and bone
IVa.	**Group 036** (Poultry Meats where MRLVD is expressed in carcass fat)		
A.	Birds sampled at slaughter	See instructions under V. Group 037	
B.	Other poultry meat	Collect 500 g of fat or sufficient product to yield 50-100 g of fat. (Normally, 1.5-2.0 kg is required.)	500 g of fat or enough tissue to yield 50-100 g of fat
V.	**Group 037** (Poultry Fats)		

[25] When adhering fat is insufficient to provide a suitable sample, the sole commodity without bone, is analyzed and the MRL will apply to the sole commodity.

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
A.	Birds sampled at slaughter	Collect abdominal fat from 3-6 birds, depending on size.	Sufficient to yield 50-100 g of fat
B.	Bulk fat tissue	Collect equal size portions from 3 locations in container.	500 g
VI.	**Group 038** (Poultry Edible Offal)		
A.	Liver	Collect 6 whole livers or a sufficient number to meet laboratory sample requirement.	250 - 500 g
B.	Other fresh/chilled or frozen edible offal product	Collect appropriate parts from 6 birds. If bulk frozen, take a cross-section from container.	250 - 500 g
VII.	**Class E - Type 16** (Secondary Meat and Poultry Products)		
A.	Fresh/chilled or frozen comminuted product of single species origin	Collect a representative fresh or frozen cross-section from selected container or packaged unit.	500 g
B.	Group 080 (Dried Meat Products)	Collect a number of packaged units in a selected container sufficient to meet laboratory sample size requirements.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
VIII.	**Class E-Type 18** (Manufactured, single ingredient product of animal origin)		
A.	Canned product (e.g., ham, beef, chicken), unit size of 1 kg or more	Collect one can from a lot. When unit size is large (greater than 2 kg), a representative sample including juices may be taken.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
B.	Cured, smoked, or cooked product (e.g., bacon slab, ham, turkey, cooked beef), unit size of at least 1 kg	Collect portion from a large unit (greater than 2 kg), or take whole unit, depending on size.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
IX.	**Class E - Type 19** (Manufactured, multiple ingredient, product of animal origin)		
A.	Sausage and luncheon meat rolls with a unit size of at least 1 kg	Collect cross-section portion from a large unit (greater than 2 kg), or whole unit, depending on size.	500 g

Appendix B

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN FISH, MILK AND EGG PRODUCTS

1. OBJECTIVE

To provide instructions for sampling a lot of eggs, milk, or aquatic animal products, to determine compliance with Codex Maximum Residue Limits for Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 Lot

An identifiable quantity of food delivered for slaughter or distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official. Several lots may make up a consignment.

2.2 Consignment

A quantity of food as described on a particular contractor's shipping document. Lots in a consignment may have different origins or be delivered at different times.

2.3 Primary Sample

A quantity of food taken from a single animal or from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one location in the lot can be combined for the primary sample.

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The bulk sample or a representative portion of the bulk sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected Class B: Primary Food Commodities of Animal Origin

Type 06 Mammalian Products

No. 033 Milks

Type 07 Poultry Products

No. 039 Eggs

Type 08 Aquatic Animal Products

No. 040 Freshwater Fish

No. 041 Diadromous Fish

No. 043 Fish Roe and Edible Offal of Fish

No. 045 Crustaceans

Type 09 Amphibians and Reptiles

No. 048 Frogs, Lizards, Snakes and Turtles

Type 10 Invertebrate Animals

No. 049 Molluscs and Other Invertebrate Animals

3.2 Selected Class E: Processed Products of Animal Origin made from only Primary Food Nos. 033, 039, 040, 041, 043, 045, 048, and 049

Type 16 - Secondary Products

Type 17 - Derived Edible Products of Aquatic Animal Origin

Type 18 - Manufactured (single ingredient) Products of a Minimum of One Kilogram Container or Unit Size

Type 19 - Manufactured (multiple ingredient) Products of a Minimum of One Kilogram Container or Unit Size

4. PRINCIPLE ADOPTED

For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each laboratory sample taken from a lot. Lot compliance with a Codex MRLVD is achieved when none of the laboratory samples contains a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to Take

During collection and processing, contamination or other changes in the samples must be prevented which would alter the residue, affect the analytical determination, or make the laboratory sample not representative of the bulk or final sample.

6.3 Collection of a Primary Sample

Detailed instructions for collection of a primary sample of various products are provided in Table B. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Table B. The following are general instructions.

a. Each primary sample should be taken from a single unit in a lot, and when possible, be selected randomly.

b. Canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. Each primary sample should contain a representative portion of juices surrounding the product. Each sample should then be frozen as described in paragraph 6.8.d.

c. Frozen product should not be thawed before sampling.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If a residue violation is suspected because of its origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport or by other relevant information to the inspection official, the lot is designated a suspect lot. If there is no reason to suspect adulteration, the lot is designated a non-suspect lot.

6.4.1 Sampling suspect lots

A minimum of six to a maximum of thirty primary samples should be collected from a suspect lot. When the suspected adulteration is expected to occur throughout the lot or is readily identifiable within the lot, the smaller number of samples is sufficient.

6.4.2 Sampling non-suspect lots

A statistically-based, random sampling programme is recommended for non-suspect lots. Any of the following types of sampling can be used.

a. Stratified random sampling

In a complex system where commodities must be sampled at many locations over extended time periods, it is very difficult to apply simple random criteria in the design of a sampling programme. A useful alternative sampling design is stratified random sampling which separates population elements into non-overlapping groups, called strata. Then samples are selected within each stratum by a simple random design. Homogeneity within each stratum is better than in the whole population. Countries or geographic regions are natural strata because of uniformity in agricultural practices. Time strata (e.g., month, quarter) are commonly used for convenience, efficiency, and detection of seasonal variability. Random number tables or other objective techniques should be used to ensure that all elements of a population have an equal and independent chance of being included in the sample.

b. Systematic sampling

Systematic sampling is a method of selecting a sample from every 'K' quantity of product to be sampled, and then sampling every 'K' unit thereafter. Systematic sampling is quicker, easier, and less costly than random sampling, when there is reliable information on product volumes to be used to determine the sampling interval that will provide the desired number of samples over time. If the sampling system is too predictable, it may be abused. It is advisable to build some randomness around the sampling point within the sampling interval.

c. Biased or estimated worst case sampling

In biased or estimated worst case sampling, the investigator should use their own judgement and experience regarding the population, lot, or sampling frame to decide which samples to select. As a non-random technique, no inferences should be made about the population sampled based on data collected. The population group anticipated to be at greatest risk may be identified.

Exporting countries should conduct a comprehensive residue testing programme and provide results to importing countries. Based on an importing country's data, testing may be conducted as applied to non-suspect products. Countries which do not provide residue testing results showing compliance with MRLVDs should be sampled as suspect lots.

6.5 Preparation of the Bulk Sample

The bulk sample is prepared by combining and thoroughly mixing the primary samples.

6.6 Preparation of the Final Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from the primary sample by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some national legislation may require the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Samples

a. Each sample or subsample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.

b. The container should be sealed so that unauthorized opening is detectable.

c. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.

d. For shipping, all perishable samples should be frozen to minus 20^{o}C, immediately after collection, and packed in a suitable container that retards thawing. If possible,

the shipping container should be placed in a freezer for 24 hours prior to packing and shipping the frozen sample.

7. RECORDS

Each sample must be correctly identified by a record with the type of sample, origin of the sample (e.g., country, state, or town), location of collection of the sample, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

TABLE B: MILK, EGGS, DAIRY PRODUCTS AND AQUATIC ANIMAL PRODUCTS

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
I.	**Group 033** **(**Milks)		
	Whole liquid milk raw, pasteurized, UHT & sterilized	In bulk. Mix thoroughly and immediately take a sample by means of a dipper. In retail containers. Take sufficient units to meet laboratory sample size requirements.	500 ml
II.	**Group 082** (Secondary Milk Products)		
A.	Skimmed milk skimmed and semi-skimmed	As for whole liquid milk.	500 ml
B.	Evaporated milk evaporated full cream & skimmed milk	Bulk containers (barrels, drums). Mix the contents carefully and scrape adhering material from the sides and bottom of the container. Remove 2 to 3 litres, repeat the stirring and take a 500 ml sample. Small retail containers. Take sufficient units to meet laboratory sample size requirements.	500 ml
C.	Milk powders		
	1. Whole	Bulk containers. Pass a dry borer tube steadily through the powder at an even rate of penetration. Remove sufficient bores to make up a sample of 500 g. Small retail containers. Take sufficient units to meet laboratory sample size requirements.	500 g
	2. Low fat	As for whole milk powders.	500 g

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
III.	**Group 087** **(**Derived Milk Products)		
A.	Cream fresh, frozen & UHT; single, whipping, whipped, double & clotted	Bulk containers. Plunge to ensure thorough mixing moving the plunger from place to place avoiding foaming, whipping and churning. Take a 200 ml sample by means of a dipper. Small containers. Take sufficient units to meet laboratory sample size requirements.	200 ml
B.	Butter including whey butter and low fat spreads containing butterfat	In bulk. Take two cores or more of butter so that the minimum total sample weight is not less than 200 g In pats or rolls. For units weighing over 250 g divide into four and take opposite quarters. For units weighing less than 250 g take one unit as sample.	200 g
C.	Butteroil including anhydrous butteroil and an- hydrous milkfat	Mix thoroughly and take a 200 g sample.	200 g
IV.	**Group 090** (Manufactured Milk Products - single ingredient)		
A.	Yoghurt natural, low fat through to full cream	Select number of units sufficient to meet laboratory requirements.	500 g
B.	Cheeses all varieties	Make two cuts radiating from the centre of the cheese if the cheese has a circular base, or parallel to the sides if the base is rectangular. The piece removed should meet the laboratory sample size requirements. For small cheeses and wrapped portions of cheese take sufficient units to meet laboratory sample requirements.	200 g
V.	**Group 092** (Manufactured Milk Products - multi- ingredient)		
A.	Dairy ice cream only ice cream containing 5% or greater of milk fat	Select block or units sufficient to meet laboratory sample size requirements.	500 ml
B.	Processed cheese preparations	Select units sufficient to meet laboratory sample size requirements.	200 g
C.	Flavoured yoghurt	As for natural yoghurt.	500 g
D.	Sweetened condensed milk	As for evaporated milk.	500 ml
VI.	**Group 039** (Eggs and Egg Products)		
A.	Liquid and frozen eggs	Use sample schedule. Subsample size will be 0.25 litre liquid or 0.5 litre packed shavings from aseptic drillings into containers.	500 g

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
B.	Dried egg products	Use sample schedule. For containers of 0.5 kg or less or 0.25 litre or less, collect a minimum of 2 units per subsample. For containers of 0.5 to 10 kg select 1 unit per subsample. for containers of 10 kg or more collect 1 kg from each unit sampled. Collect with aseptic technique.	500 g
C.	Shell eggs		
	1. Retail packages	Use sample schedule. Subsample size is 1 dozen.	500 g or 10 whole eggs
	2. Commercial cases	For 15 cases or less collect 1 dozen from each case, minimum of 2 dozen eggs. For 16 or more cases collect 1 dozen from 15 random cases.	500 g or 10 whole eggs
VII.	**Class B - Type 08** (Aquatic Animal Products)		
A.	Packaged fish fresh, frozen, smoked, cured, or shellfish (except oysters)	Collect 12 subsamples randomly. Minimum subsample size is 1 kg.	1000 g
B.	Bulk fish 0.5 - 1.5 kg	Collect 12 subsamples randomly. Each subsample should total 0.5 kg of edible fish.	1000 g
C.	Bulk shellfish (except oysters)	Collect 12 subsamples randomly.	1000 g
D.	Other fish and shellfish products (including oysters)	Collect 12 - 0.25 litre subsamples.	1000 g
VIII.	**Class E - Type 17** (Derived Edible Products of Aquatic Animal Origin)		
A.	Canned fish and shellfish products (except oysters)	Collect 12 subsamples of 5 cans per subsample.	1000 g
B.	Other fish and shellfish products - fish flour and meal	Use sample schedule. Collect 1 kg per subsample.	1000 g

Appendix C

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN HONEY

1. OBJECTIVE

To provide instructions for sampling a lot of honey to determine compliance with Codex Maximum Residue Limits for Residues of Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 Lot

An identifiable quantity of food (honey) delivered for distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official. Several lots may make up a consignment.

2.2 Consignment

A quantity of food (honey) as described on a particular contractor's shipping document. Lots in a consignment may have different origins or may be delivered at different times.

2.3 Primary Sample

A quantity of honey taken from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one location can be combined for the primary sample.

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The bulk sample or a representative portion of the bulk sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected According to Origin

Blossom or nectar honey that comes mainly from nectaries of flowers.

Honeydew honey that comes mainly from secretions of or on living parts of plants.

3.2 Selected According to Mode of Processing

Comb honey that is stored by bees in the cells of freshly built broodless combs, and sold in sealed whole combs or sections of such combs.

Extracted honey that is obtained by centrifuging decapped broodless combs.

Pressed honey that is obtained by pressing broodless combs with or without the application of moderate heat.

4. PRINCIPLE ADOPTED

For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each laboratory sample taken from a lot. Lot compliance with a Codex MRLVD is achieved when none of the laboratory samples contain a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to Take

During collection and processing, contamination or other changes in the samples must be prevented which would alter the residue, affect the analytical determination, or make the laboratory sample not representative of the bulk or final sample.

6.3 Collection of a Primary Sample

Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements and detailed instructions for collection of a primary sample of honey are provided in Appendix C, paragraph 9. The following are general instructions.

a. Each primary sample should be taken from a single unit in a lot, and when possible, be selected randomly.

b. Packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. The primary sample should contain a representative portion of the product. Each sample should be prepared for analysis as referenced in paragraph 6.5.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If adulteration is suspected by origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport or by the availability of other relevant information to the inspection official, the lot is designated a suspect lot. If there is no reason to suspect adulteration, the lot is designated a non-suspect lot.

6.5 Preparation of the Primary Sample

The primary sample is prepared as described in paragraph 9.

6.6 Preparation of the Laboratory Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from it by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some national legislation may require that the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Primary Samples

a. Each primary sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.

b. The container should be sealed so that unauthorized opening is detectable.

c. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.

7. RECORDS

Each primary sample should be correctly identified by a record with the type of sample, its origin (e.g., country, state, or town), its location of collection, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

9. SAMPLING INSTRUCTIONS

9.1 Liquid or Strained Honey

If sample is free from granulation, mix thoroughly by stirring or shaking; if granulated, place closed container in water-bath without submerging, and heat 30 min at 60°C; then if necessary heat at 65°C until liquefied. Occasional shaking is essential. Mix thoroughly and cool rapidly as soon as sample liquefies. If foreign matter, such as wax, sticks, bees, particles of comb, etc., is present, heat sample to 40°C in water-bath and strain through cheesecloth in hot-water-funnel before sampling.

Collect 250 ml of liquid or strained honey.

9.2 Comb Honey

Cut across top of comb, if sealed, and separate completely from comb by straining through a sieve the meshes of which are made by so weaving wire as to form square opening of 0.500 mm by 0.500 mm (ISO 565-1983)[26]. When portions of comb or wax pass through sieve, heat samples as in paragraph 9.1 and strain through cheesecloth. If honey is granulated in comb, heat until wax is liquefied; stir, cool and remove wax.

Collect 250 ml of liquid honey.

[26] Such sieve could be replaced by US sieve with No. 40 standard screen (size of opening 0.420 mm).

PART II

GENERAL CONSIDERATIONS ON ANALYTICAL METHODS FOR RESIDUE CONTROL

It would be ideal to have analytical methods available for determining compliance with MRLVDs that are effective and practical to detect, quantify, and identify all residues of veterinary drugs and pesticides (used as veterinary drugs) that may be present in commodities within the terms of reference of this Codex Committee. These methods could be routinely used by regulatory control authorities of member governments for their residue testing programmes to assure compliance with food safety requirements.

Methods with the capabilities mentioned above are not available for many compounds of interest because of the extensive number of potential veterinary drug residues which may find their way into food within the terms of reference of the CCRVDF. To optimize the effectiveness of regulatory programmes to test for veterinary drug residues, residue control programmes must use available residue methodology to assure compliance with Codex MRLVDs and, as necessary, take appropriate regulatory action against adulterated products, consistent with the reliability of the analytical data.

To assist regulatory authorities in determining their analytical needs for residue control programmes, this document will describe the types of methods available and a set of attributes which residue control programmes may utilize in carrying out their missions.

The principal attributes of analytical methods for residue control programmes are specificity, precision, accuracy (measured as systematic error and recovery), and sensitivity. Determining these principal attributes in a method requires well designed multi-laboratory studies. The attributes noted above will be presented in a subsequent section of this paper in more detail.

TYPES OF ANALYTICAL METHODS

Several types of methods are available to food safety agencies and programmes to conduct analyses that are consistent with the needs of residue testing programmes. Decisions on the use of a specific analytical method depends on the intended objectives of the regulatory programme and the analytical performance characteristics of methods.

Methods that are suitable for determining compliance with MRLVDs are those that have successfully completed an extensive multi-laboratory study for specific tissue and species combinations. These methods provide analytical results for either quantitation or identification that are appropriate to take regulatory action without the need for additional analyses. In some cases, these methods may be considered reference methods, but reference methods frequently are not routine.

Many methods currently being used by residue control programmes have successfully completed a multi-laboratory study. Multi-laboratory method performance studies generally satisfy these analytical requirements. Validated methods are those subjected to a properly designed inter-laboratory study with three or more analysts, and preferably, in three different laboratories. Collaborative study methods have successfully completed method evaluation in six or more laboratories in an acceptable, statistically designed study. Some residue control methods that have demonstrated their usefulness for determining compliance with MRLVDs have an historical origin. These history based methods were considered to be the best available at the time of initial regulatory

use and have continued in use over an extended period of time in the absence of more effective validated methods.

Collaborative study and validated methods may be extended to additional tissues, species, products, or combinations of these, not included in the original multi-laboratory study by completing additional properly designed laboratory studies. On a case by case basis, analytical results from method extension studies may require additional analysis and/or review before reporting results or taking regulatory action.

Methods that have not been validated by traditional inter-laboratory study, but provide results that may be correlated and compared with data obtained from a collaborative study or validated method, may serve a regulatory purpose. The validated and non-validated methods must be compared in a statistically acceptable study design using portions of the same (homogeneous) samples prepared for this comparison. The data from these studies should be reviewed by a peer group of regulatory scientists to determine the comparability of method performance.

There are some non-routine veterinary drug residue methods suitable for enforcement of MRLVDs. These methods may not have been subjected to an inter-laboratory study because they require specialized expertise or equipment. Good quality control and quality assurance procedures must be applied with these methods. Analytical data obtained from these methods should be reviewed by a peer group of regulatory analysts before recommending any regulatory action. These analytical methods may require analysis by another method to corroborate the initial experimental findings.

Occasionally, a method may be suitable for Codex purposes because the toxicology of an analyte does not allow an MRLVD to be established. Methods for analytes such as chloramphenicol would be in this category. Some methods in this category will include those presented above which are not sufficiently sensitive to quantitate and/or identify analyte(s) at or below the MRLVD. Such methods also may not meet other performance factors stated above.

There are some methods for which additional analysis is required to support regulatory action. This category may include methods that do not provide adequate information of structure or residue concentration. Analytical methods that may have been subjected to ruggedness testing, but not successfully to a multi-laboratory study to evaluate method performance, may have limited usefulness in a residue control programme. However, these methods may be useful in non-recurring or infrequent residue analyses, but they commonly require use of a rigorous protocol for sample analysis. Results from such methods should be considered only as estimates of analyte concentration or identification without additional supporting analytical information. Results from these methods can be useful for gathering residue information and determining whether there is a need to develop a more definitive method. These methods should not be used alone for residue control purposes on official samples without additional information (e.g., such as the presence of an injection site in the sample).

Certain methods may only be suitable for determining whether or not a veterinary drug residue problem exists in a sampling population. Methods in this category are used for information gathering, or exploratory residue control studies. Exploratory studies may also be undertaken using methods which have not been subjected to inter-laboratory study. These non-routine methods may be complex, or require highly specialized instrumentation, and may have been developed and used only in a single laboratory. Analytical results from these methods should not be used independently for taking regulatory action, but may be used to determine the need for additional testing and/or development of a method suitable for routine enforcement of MRLVDs.

Methods designed to analyze large numbers of samples quickly may be useful for determining the presence or absence of one or more compounds in a quantitative or semi-quantitative manner, at or above a specified concentration. Results at or above the MRLVD commonly require additional

analysis using a method with acceptable performance characteristics before taking regulatory action. Results from methods of this type that are below the MRLVD but above a level of reliable measurement of a more definitive method, may have limited use in determining exposure patterns.

METHOD DEVELOPMENT CONSIDERATIONS

Developing an analytical method requires analysts, laboratory space, equipment, and financial support. To optimize the benefit of these resources, it is important to provide introductory and background information to establish a perspective for planning an analytical method development project, and for evaluating the performance of the analytical method.

Residue control programmes should use methodology suitable to the analytes of interest to assure a safe and wholesome food supply. Necessary and appropriate regulatory action should be taken against adulterated products, consistent with the reliability of the analytical data. Before initiating method development activities, the intended use and need for a method in a residue control programme should be established. Other considerations include the compound or class of compounds of interest (and potential interfering substances), potential measurement systems and their properties, the pertinent physical and chemical properties that may influence method performance, the specificity of the desired testing system and how it was determined, analyte and reagent stability data and purity of reagents, the acceptable operating conditions for meeting method performance factors, sample preparation guidelines, environmental factors that may influence method performance, safety items, and any other specific information pertinent to programme needs.

ANALYTICAL PERFORMANCE CHARACTERISTICS

Specificity is the ability of a method to distinguish between the analyte of interest and other substances which may be present in the test sample. A residue control method must be able to provide unambiguous identification of the compound being measured. The ability to quantitatively differentiate the analyte from homologues, analogues, or metabolic products under the experimental conditions employed is an important consideration of specificity.

Precision of a method is the closeness of agreement between independent test results obtained from homogeneous test material under the stipulated conditions of use. Analytical variability between different laboratories is defined as reproducibility, and variability from repeated analyses within a laboratory is repeatability. Precision of a method is usually expressed as standard deviation. Another useful term is relative standard deviation, or coefficient of variation (the standard deviation, divided by the absolute value of the arithmetic mean). It may be reported as a percentage by multiplying by one hundred. Method variability achieved in the developing laboratory after considerable experience with a method, is usually less than the variability achieved by other laboratories that may later also use the method. For this reason, analytical data from a method should be statistically analyzed by procedures described by Youden and Steiner (Ref: Statistical Manual of the AOAC, AOAC INTERNATIONAL, Gaithersburg, MD, 1975) before preparing a final method write up. If a method cannot achieve a suitable level of performance in the developing laboratory, it cannot be expected to do any better in other laboratories.

Accuracy refers to the closeness of agreement between the true value of the analyte concentration and the mean result that is obtained by applying the experimental procedure a large number of times to a set of homogeneous samples. Accuracy is closely related to systematic error (analytical method bias) and analyte recovery (measured as percent recovery). The accuracy requirements of methods will vary depending upon the planned regulatory use of the results. Generally, the accuracy at and below the MRLVD or level of interest must be equal to or greater than the accuracy above the level of interest.

The percent recovery of analyte added to a blank test sample is a related measurement that compares the amount found by analysis with the amount added to the sample. In interpreting recoveries, it is necessary to recognize that analyte added to a sample may not behave in the same manner as the same biologically incurred analyte (veterinary drug residue). At relatively high concentrations, analytical recoveries are expected to approach one hundred percent. At lower concentrations and, particularly with methods involving a number of steps including extraction, isolation, purification, and concentration, recoveries may be lower. Regardless of what average recoveries are observed, recovery with low variability is desirable.

The sensitivity of a method is a measure of its ability to detect the presence of an analyte and to discriminate between small differences in analyte concentration. Sensitivity also requires the ability to differentiate between analyte, related compounds and background interferences. For analytical instruments used in residue analysis, sensitivity is determined by two factors: instrumental response to the analyte and background interference, or instrument noise. Response is measured by the slope of the calibration curve with analyte standards at concentrations of interest. An ideal situation would be afforded by a linear curve. Instrument noise is the response produced by an instrument when no analyte is present in the test sample.

There are a number of collateral attributes suitable for analytical methods for regulatory control programmes beyond these principle method attributes. Methods should be rugged or robust, cost effective, relatively uncomplicated, portable, and capable of simultaneously handling a set of samples in a time effective manner. Ruggedness of a method refers to results being relatively unaffected by small deviations from the optimal amounts of reagents used in the analytical method, time factors for extractions or reactions, or temperature. This does not provide latitude for carelessness or haphazard techniques. Cost-effectiveness is the use of relatively common reagents, instruments, or equipment customarily available and used in a laboratory devoted to veterinary drug residue analyses. An uncomplicated method uses simple, straightforward mechanical or operational procedures throughout the method.

Portability is the analytical method characteristic that enables it to be transferred from one location to another without loss of established analytical performance characteristics.

The capability of a residue control method to simultaneously analyze a set of samples aids in method efficiency by allowing sets or batches of samples to be analyzed at the same time. This attribute reduces the analytical time requirements of sample analysis. It provides, for example, the capability of completing four or more analyses in a normal working day. This is important when large numbers of samples must be analyzed in short or fixed time frames.

Establishing method performance attributes is very important. These attributes provide the necessary information for food safety agencies to develop and manage their public health programmes. Performance attributes for analytical methods also provide a basis for good management decisions in future planning, evaluation, and product disposition. For the animal health care industry, it provides a guideline for knowing exactly what performance must be achieved in developing analytical procedures. All will benefit by having well defined analytical method performance factors.

INTEGRATING ANALYTICAL METHODS FOR RESIDUE CONTROL

Residue control and standard setting organizations have different terminologies to describe application of analytical methods. Methods of analysis for veterinary drug residues in foods must ultimately be able to reliably detect the presence of an analyte of interest, determine its concentration, and correctly identify the analyte at and above an established maximum residue limit (MRLVD) for regulatory enforcement actions to be taken. The latter methods would be classified as confirmatory

methods. These confirmatory methods may or may not have a quantitative or semi-quantitative component.

Other types of methods that may be used in residue control programmes, and which can strengthen such a programme, may be classified into two additional categories. These categories are quantitative methods and screening methods. Quantitative methods provide precise information concerning the amount of an analyte that may be present, but may only provide indirect information about the structural identity of the analyte. Screening methods may quickly determine the presence of one or more compounds, based upon one or more common characteristic of a class of veterinary drugs in a qualitative or semi-quantitative manner at a specified concentration limit. They may also determine that an analyte is below the limit of detection of the screening method.

These three categories of methods, confirmatory, quantitative, and screening, often share a common set of performance characteristics described above. In addition, they may have other specific considerations. Understanding the relationship between these three categories of methods is important in the development and operation of a balanced residue control programme. Screening methods are useful because they provide greater analytical efficiency (i.e., a greater number of analyses may be performed in a given time frame) than quantitative and/or confirmatory methods. In many circumstances screening methods can be performed in non-laboratory environments. Screening methods suitable for use in non-laboratory environments may be less expensive for regulatory control programmes than conducting all testing within a laboratory setting. Screening methods can be to separate test samples with no detectable residue from those that indicate the presence of a veterinary drug residue at or below an MRLVD or an appropriate level of interest. This would allow a laboratory to focus more of its efforts on quantitation of the presumptive positive test samples of regulatory interest.

Screening tests may also be used efficiently in a laboratory setting because they analyze a larger numbers of samples in a given time frame than their corresponding quantitative methods. The cost savings may not be as great as when screening methods are used in non-laboratory environments because the costs associated with the handling and shipping of samples must still be incurred. Presumptive positive results obtained from laboratory screening methods should not be used independently in taking regulatory action. Data obtained from such methods may be used to determine the need for additional testing and/or the development of a method suitable for routine enforcement of MRLVDs.

METHOD DEVELOPMENT AND VALIDATION CONSIDERATIONS FOR RESIDUE CONTROL METHODS

The multi-laboratory method validation study is the most important factor in providing analytical data to define method performance characteristics.

In developing a residue control method, whenever possible, data should be collected from three types of samples. Control test material from non-treated animals provides information about analytical background and matrix interferences. Fortified test material, containing known amounts of the analyte added to the control material, yields information about the method's ability to recover the analyte of interest under controlled conditions. Dosed or biologically incurred tissue, from food producing animals and birds that have been treated with the drug, provide additional analytical performance information about biological or other interactions that may occur when analyzing residue control samples.

Residue methods should be designed with as much simplicity as possible. Analytical simplicity helps minimize the variety, size, and type of glassware and equipment needed, minimizes the potential for analytical errors, and reduces laboratory and method costs. Reagents and standards

must be available commercially or from some other reliable source. Instrumentation should be selected based on its performance characteristics rather than a particular manufacturer.

Residue methods are sometimes designed using internal standards for analytical control. A properly used internal standard will compensate for some of the analytical variability of an analysis, improving precision. However, an improperly used internal standard may obscure variables that are an important part of the analytical measurement. If an internal standard is used, it should be added to a sample as early as possible in the procedure, preferably to the test material before analysis begins. Caution must be taken in the choice of internal standards to ensure that they do not alter the percent recovery of the analyte of interest or interfere with the measurement process. It is important to know the extent and predictability of the effects of the internal standard on an analytical method. Internal standards can greatly enhance method performance when used properly.

Residue control methods that may be subjected to widely variable physical test environments will place some additional requirements on methods. Addressing these may help improve method ruggedness. Warmer environments may require reagents to be more thermally stable, while solvents used in the analysis will have to be less volatile, and test sample requirements to be more lenient. Cooler environments may require reagents and solvents to have different physical properties, such as lower freezing point and greater solvating characteristics, to ensure effective extraction of an analyte. Environmental temperatures may influence the time required to perform an analysis, as well as influencing reaction rates, gravitational separations and colour development. These considerations may strain efforts to standardize methods for use in broadly differing environments because of the need to adapt methods to compensate for these factors.

An analytical method developed and used in only one laboratory may have limited use in a residue control programme. The reliability of reported values may be a concern even though strong quality control procedures may have been employed. As a minimum, three laboratories expected to use these methods should be used to develop performance characteristics for residue control, including analytical variability, and obtain statistically acceptable agreement on the same samples divided among the testing laboratories. Methods with higher reliability for residue testing should be able to successfully undergo a collaborative study involving at least six different laboratories (Ref: *Use of Statistics to Develop and Evaluate Analytical Methods* (by G.T. Wernimont and W. Spendley, AOAC INTERNATIONAL, Gaithersburg, MD), and *Compound Evaluation and Analytical Capability National Residue Programme Plan 1990*, (section 5, USDA, Food Safety and Inspection Service, Washington, D.C.)).

The principles for conducting either a validation or collaborative study of a residue control method are the same. Samples for evaluating method performance should be unknown to the analyst, contain the residue near the MRLVD as well as samples with the analyte above and below the level of interest, and test material blanks. All study samples should be analyzed over a limited number of days, preferably with replicate analysis, to improve statistical evaluation of method performance. It should be noted that these are only minimal requirements. Duplicate analyses in only six laboratories with one or two animal species and tissues would yield limited quality estimates for repeatability and reproducibility.

Quality control and quality assurance principles are essential components of residue analysis. They provide the basis for ensuring optimum method performance for all methods, regardless of method attributes, whenever they are used. Quality control monitors those factors associated with the analysis of a sample by a tester, while quality assurance provides the oversight by independent reviewers to ensure that the analytical programme is performing in an acceptable manner. Quality control and quality assurance programmes are invaluable to support decision-making for residue control agencies, improving the reliability of analytical results, and providing quality data for residue

control programmes to demonstrate food safety to consumers, producers, and law making bodies regarding residues of veterinary drugs in food.

PART III

ATTRIBUTES OF ANALYTICAL METHODS FOR RESIDUES OF VETERINARY DRUGS IN FOODS

The performance characteristics of analytical methods for determining compliance with MRLVDs must be defined and proposed methods evaluated accordingly. This will ensure reliable analytical results and provide a secure basis for determining residues of veterinary drugs in foods for commodities in international trade. Part II, *General Considerations of Analytical Methods for Regulatory Control*, presents a discussion of general types or categories of regulatory methods, and provides a scheme for using these analytical methods based upon their intended purpose in a regulatory framework. In the discussion below, attributes common to three categories of methods for determining compliance with Codex MRLVDs referred to as Level I, Level II and Level III methods will be presented followed by additional attributes that are applicable to only one or two categories of methods.

(**Note**: This Part contains numerous definitions. The CCRVDF has attempted to harmonize these definitions with those provided in the "Definitions for the Purpose of the Codex Alimentarius" in Volume 1.)

GENERAL CRITERIA FOR ATTRIBUTES

All methods may be characterized by a set of attributes or properties that determine their usefulness: *specificity* - what is being measured; *precision* - the variability of the measurement; and *systematic error* or *bias* - measured as analytical recovery. Another attribute, *accuracy*, usually refers to the closeness of agreement, or trueness of an analytical result, between the true value and the mean value obtained by analyzing a large number of samples of the test material. For semi-quantitative methods and screening methods, accuracy may also be defined as a measure of false negative and false positive responses. The *limit of detection*, *method sensitivity*, *practicality of use*, *tissue/species applicability*, *limit of detection* and *limit of quantitation* are additional attributes that have varying relevance to some methods, depending upon the intended use of the analytical results.

Methods may be described according to performance attributes as an alternative to classifying them by intent of use or purpose. This alternative approach defines methods by the analytical information and detail provided concerning the amount and nature of the analyte(s) of interest. Level I methods are the most definitive, while Level III methods usually provide general information about the presence of an analyte and semi-quantitative information about the amount of material present.

Level I methods quantify the amount of a specific analyte or class of analytes and positively identify the analyte, providing the greatest amount of reliability for quantitation and structure identification of the analyte at the level of interest. These methods may be a single procedure that determines both the concentration and identity of the analyte, or a combination of methods to quantify and confirm the structure of a veterinary drug residue. A good example of the latter is a chromatographic technique combined with a mass spectrometry procedure. Although Level I methods are generally instrumental procedures, observation of a pathologic or other morphologic change that specifically identifies exposure to a class of veterinary drugs, could potentially be a Level I method, if it has sufficient sensitivity and precision.

Level I methods may be limited to analytes with appropriate physical and chemical properties amenable to chromatographic and other instrumental methods of analysis. For example, at the present time, there are very few antibiotic drugs for veterinary use that have mass spectrometric procedures useful to determine compliance with MRLVDs because of the relatively low volatility and stability of

antibiotic drugs to chemical techniques commonly employed for mass spectrometry analysis. However, new technology and instrumentation is now making development of these confirmatory methods possible. Level I methods are sometimes referred to as reference methods.

Level II methods commonly determine the concentration of an analyte at the level of interest, but do not provide unequivocal structure identification. These methods may use structure, functional group, or immunological properties as the basis for the analytical scheme. A common practice is to use one Level II method as the determinative assay and a second Level II method as the positive identification procedure. These methods may also be used to verify the presence of a compound or class of compounds. Two Level II methods may provide information suitable for a Level I method, when they use different chemical procedures. The majority of analytical methods commonly used to support MRLVDs are quantitative Level II laboratory methods.

Level III methods are those that generate less definitive but useful information. These testing procedures generally determine the presence or the absence of a compound or class of compounds at some designated level of interest. They are often based on non-instrumental techniques. For these reasons, Level III methods are commonly referred to as screening or semi-quantitative methods. Results on a given sample are not as reliable as Level I or II methods and usually need corroborating information for regulatory action. For example, Level III methods may provide good semi-quantitative information, but poor identification. Alternatively, they may provide strong or unequivocal identification with very little quantitative information. Level III methods are not poorly described or sloppy methods. They must have a well-defined operating protocol, operating characteristics and performance data.

Many of the microbiological agar plate assay procedures, enzyme inhibition assays and immunology based systems are in this category. They are useful for residue control programmes because of their high sample capacity, portability, convenience and potential suitability to non-laboratory environments. The limitation of Level III type methods is that action based on individual positive results usually requires verification using Level I or II methods. Individual results may be verified by epidemiological information.

Level III methods may offer substantial advantages to a residue control programme. Their advantages include analytical speed, sample efficiency through batch analysis, portability to non-laboratory environments, good sensitivity, or the ability to detect classes of compounds. Even though a Level III method may not detect a specific compound at a regulatory limit (i.e., an MRLVD) with every sample, it may be better than relying on Level I and II methods because of their ability to test more samples.

The decision to use Level III methods should be determined in part by performance characteristics, as well as the need to test large numbers of samples within a given time frame. Two key characteristics to consider for Level III methods are the percent false positives and percent false negatives, determined by comparison with a validated quantitative assay in a statistically designed protocol. The percent false negatives must be quite low at the levels of interest, while slightly more flexibility may be acceptable for false positives. Residue detection limits can be described based on these two parameters.

METHOD ATTRIBUTES

Specificity is the ability of a method to distinguish between the analyte being measured and other substances which may be present in the test material. A proposed method also must provide the required specificity for the compound being measured and discriminate between other structurally similar substances. This characteristic is predominately a function of the measuring principle or detection system used. Certain instrumental techniques such as Fourier transform infrared

spectroscopy or mass spectrometry may be sufficiently specific by themselves to provide unambiguous identification. These are often referred to as confirmatory methods. Positive identification from a confirmatory method is usually considered necessary before regulatory action is taken in those instances when an analytical result is not sufficiently specific for regulatory purposes. Confirmatory methods may be considered Level I methods when they provide a determinative result to quantify and tentatively identify a given analyte, and a procedure which verifies the identity of the analyte of interest.

Other techniques, when they are used in combination, may be capable of achieving a comparable degree of specificity as confirmatory techniques. For example, specificity may be verified by combinations of methods such as thin layer chromatography, element-specific gas-liquid chromatography and accompanying detection systems, formation of characteristic derivatives followed by additional chromatography, or determining compound specific relative retention times using several chromatographic systems of differing polarity. Such procedures must be applicable at the designated maximum residue limit (MRLVD) of the analyte.

The specificity of a screening method normally is not as great as that of a determinative method, because screening methods often take advantage of a structural feature common to a group or class of compounds. These methods generally fit into the Level III methods category. Techniques based on biological assays, immunoassays, or chromogenic responses are not expected to be as specific as those techniques which unequivocally identify a compound. Specificity of a screening method may be increased by the use of chromatographic or other separation technique.

If a non-specific response or some ambiguity in a test result is obtained (i.e., cross-reactivity with components of the matrix other than that for which the analysis was designed), studies that approximate the concentration of the non-specific response of the analytical method may be required to identify the compounds that respond to the detection system. If the method is not sufficiently specific, then a confirmatory or identification procedure will be needed to characterize the analyte of interest.

Precision is an important performance characteristic of residue control methods. This attribute is common to all methods, and as noted below, acceptable precision may not be a function of the type of method, but of the concentration of the analyte in the original sample. There are several types of precision. Inter-laboratory precision, or reproducibility, is the closeness of agreement between test results obtained with the same method on identical test material in different laboratories. The variation in replicate analyses of a test material within a laboratory when performed by one analyst is repeatability. The intra-laboratory variability among analysts performing the same analysis is within-laboratory bias, and is primarily due to random error. Precision is usually expressed as a standard deviation (an absolute value determined experimentally). More useful is the relative standard deviation, or coefficient of variation. This parameter expresses variability as a function of concentration, and is relatively constant over a given concentration interval.

Precision limits for analytical methods, as a function of concentration, are presented below. The recommended values take into consideration the wide variety of methods, analytes, matrices, and species within the terms of reference of the Committee and that are usually applied in a broad-based residue control programme.

Concentration	Coefficient of Variability (CV) (Repeatability)
≤ 1 µg/kg	35%
≥ 1 µg/kg ≤ 10 µg/kg	30%
≥ 10 µg/kg ≤ 100 µg/kg	20%
≥ 100 µg/kg	15%

The variability achieved in the laboratory where a method was developed, and where there is considerable experience, is usually smaller than that attained by laboratories that may later use the method and have less experience with it. The final version of the method should be optimized by using procedures such as ruggedness testing to identify its critical control points and ensure that its performance will not be adversely affected by small changes in using the analytical procedure. If a method cannot achieve acceptable performance in the sponsor's laboratory, its performance usually will not be any better in other laboratories.

When developing analytical data to be used to define expected method variability and other performance characteristics, methods should be performed by an analyst who has not been directly involved in developing the method. This procedure will verify the adequacy of the method's written description and help identify critical parameters which affect method performance.

The within laboratory coefficient of variation should be ≤15 percent when the designated concentration of the analyte is greater than or equal to 100 µg/kg. When the designated concentration of the analyte is 10 - 100 µg/kg, the within laboratory coefficient of variation should be ≤20 percent. When the concentration of interest is below 10 µg/kg, a coefficient of variation of ≤30 percent is acceptable.

A Level III method should be capable of identifying samples that contain a residue concentration at the level of interest. When a sample contains a residue that exceeds the MRLVD using a semi-quantitative (screening) method, regulatory action requires additional analysis. In this situation, the sample will require analysis using a determinative method and a confirmatory method with defined performance characteristics. A useful attribute for Level III methods is its precision at and just below the MRLVD. Precision may be somewhat less important above the MRLVD.

Systematic error, or method bias, is the difference between the experimentally determined (measured) value and the mean result that would be obtained by applying the experimental procedure a very large number of times to the test material. Systematic errors are always of the same sign and magnitude. Random error, however, is variable in magnitude and sign and the mean of random errors may approach zero if sufficient samples are tested. Accuracy is generally expressed as the percent recovery of the analyte of interest. Recovery is obtained experimentally by adding known quantities of the analyte directly to separate portions of the test material and comparing the amount recovered with the amount added. The percent recovery of an analyte added directly to the sample matrix is generally a higher value than is obtained experimentally when isolating the same biologically incurred analyte from a given sample matrix. At relatively high analyte concentrations, recoveries are expected to approach 100 percent. At lower concentrations or with multi-step methods that require extractions, solvent transfers, concentration steps, and absorption chromatography, recoveries will be lower. Variability of analyte recovery is usually as important as the percent recovery itself and should be small.

Average recoveries of 80 to 110 percent should be obtained when the MRLVD for the analyte is 100 µg/kg or greater and when the analytical method can be performed with acceptable precision.

Recommended acceptable recoveries at lower MRLVDs are 70 to 110 percent when the MRLVD is 10 µg/kg to 100 µg/kg, and 60 to 120 percent when the MRLVD is less than 10 µg/kg. These recovery limits are reasonable when viewed within the context of the wide variety of residues, methods, matrices, and species normally included in a broad-based residue testing programme. Variability in recovery should be small regardless of the percent recovery.

Correction factors for more or less than 100 percent recovery may be appropriate when analytical methods use isotope dilution procedures or other appropriate internal reference standards for quantitation purposes.

The accuracy requirements of different types of methods will vary with the intended use for the results. In general, methods should have their greatest accuracy at the MRLVD. The accuracy requirements of confirmatory methods may not be as great as is required for quantitative methods, because in most residue control programmes these methods are only performed after a residue concentration greater than the MRLVD has been determined by a quantitative method. Most confirmatory methods have a quantitative aspect built into them which serves as an additional check on the previously performed quantitative method. Suggested accuracy requirements for methods are given below, and are based upon the previously stated considerations of a broad-based residue testing programme.

Concentration	Acceptable range
≤ 1 µg/kg	-50 to +20%
≥ 1 µg/kg ≤ 10 µg/kg	-40 to +20%
≥ 10 µg/kg ≤ 100 µg/kg	-30 to +10%
≥ 100 µg/kg	-20 to +10%

Level III methods may be useful for residue control programmes in several scenarios. For example, they may be used in situations where no MRLVD can be established or where one does not otherwise exist, and regulatory action may be taken if any amount of the drug residue is found. Non-quantitative methods may also be used when the MRLVD or the level of interest is less than the limit of detection of the screening method. In both cases, it is necessary to evaluate proposed methods for the specified residue test to experimentally determine the lowest concentration at which an analyte can be detected and to determine method accuracy and limits by using data on false negatives (i.e., a negative analytical result is obtained when the analyte is present), and false positives, (i.e., a positive result is obtained when the analyte is not present) at or above the MRLVD.

If Level III methods involve a manufactured test kit, at a minimum, the accuracy, precision, specificity and lowest detection limit data should be provided by the manufacturer. The users should verify the validity of this data through their own studies and evaluate performance by quality control checks. The lowest detectable concentration of an analyte should represent the smallest amount of an individual analyte that can be reliably observed or found in the test sample. The method accuracy, expressed in terms of false negatives and false positives, should be determined by a statistically valid, scientifically correct study with appropriate controls.

In general, non-quantitative methods should produce less than 5 percent false negatives and less than 10 percent false positives when analysis is performed on the test sample. These values may vary depending on the type of action that will be taken as a result of the analytical test. Conservative values should be chosen appropriate to residue testing needs.

The limit of detection is the smallest measured concentration of an analyte from which it is possible to deduce the presence of the analyte in the test sample with acceptable certainty. This determination should consider matrix related interferences with an instrumental signal to noise (S/N) ratio greater than 5:1 or the concentration determined by a factor of 3 standard deviations of the signal response for blank tissue, whichever is less.

Sensitivity is a measure of the ability of a method to detect the presence of an analyte and to discriminate between small differences in analyte content. This may be determined by the slope of the standard curve at concentrations of interest.

COLLATERAL PARAMETERS FOR METHODS SUITABLE FOR ROUTINE USE FOR ENFORCEMENT OF MAXIMUM RESIDUE LIMITS

Residue control methods should be capable of analyzing several samples simultaneously, normally in groups of four or more during a normal work period. These methods should ideally require no more than about 2 hours of analytical time per sample. This does not require that results for a set of analytical samples must be completed within 2 hours. Several hours may be necessary to prepare a set of extracts or complete a microbiological incubation, for example, before analysis of test sample results can be completed. Regulatory methods should be able to be completed within reasonable time periods consistent with regulatory objectives.

The applicability of a method refers to the tissue matrices and animal species that a particular method has demonstrated acceptable method performance for compliance with an MRLVD.

The limit of quantitation corresponds to the smallest measured concentration of residue from endogenously incurred test material above which a determination of the analyte can be made with a specified degree of certainty to its accuracy and precision.

For determining compliance with an MRLVD, an analytical method should require only instrumentation generally available in a laboratory devoted to trace analyses in the appropriate test material. The methods should be capable of analyzing analytes at or below the MRLVD. In addition, the methods should have written protocols that include extensive quality assurance and quality control components. These quality assurance plans should also include analyst training needs.

Whenever applicable, methods should be evaluated in an inter-laboratory study using some test samples with biologically incurred analyte. Experience suggests that using biologically incurred residues for method evaluation provides a better description of the expected performance characteristics of the method as it would be used routinely by regulatory authorities.

Residue testing methods must demonstrate that they can be performed at their described performance characteristics by experienced analysts who have received adequate method training. Acceptable methods performance can be demonstrated by successfully analyzing sets of samples containing the analyte of interest in sample matrices within the scope of the CCRVDF terms of reference.

Methods to determine compliance with MRLVDs should utilize commercially available reagents and equipment. Methods may become impractical and potentially unreliable if new or unusual reagents are not readily available. New or unusual reagents and standards must be assured by the method sponsor upon request.

Regulatory methods for residue control should not use large quantities of solvents, reagents, and supplies which would render the method economically impractical. Methods for determining compliance with Codex MRLVDs should be designed for safe performance by trained analysts.

Several other indicators of satisfactory performance may be helpful in determining whether or not a method is acceptable for Codex purposes. These include: (a) calibration (standard) and analytical (recovery) curves; (b) information on the effectiveness of extraction for removing specific potential interferences; (c) adequate method sensitivity (slope of the standard calibration curve) with a linear dynamic range at the concentration of interest; (d) adequate resolution from matrix components; (e) sufficiently low and reproducibly consistent blanks; and (f) stability studies performed on the matrix, the analyte within the matrix, and reagents used in the procedure. The analytical response of the blank should be no more than 10% of the analyte response at the MRLVD, whenever an MRLVD is established. Critical control points within the analytical procedure, those steps where extreme care must be taken to insure optimum method performance, and stopping points within the method need to be identified and noted in the written procedure.

SPECIFIC DATA NEEDED

The developer of a method must provide pertinent information and supporting data necessary to familiarize other intended users of a method so they can achieve satisfactory methods performance. This necessary information should include the following:

For Codex methods, the developer of a method should collect and provide data from three types of samples: (a) control tissue samples from animals that are known not to have been exposed to the analyte; (b) tissue samples that are fortified or spiked at the levels of interest by the addition of known amounts of the analyte to uncontaminated control tissue; and (c) dosed or incurred tissue samples at the concentration of interest (MRLVD) obtained from animals treated with the veterinary drug according to good veterinary practices.

Methods provided by developers, drug sponsors and commercially available test kits intended for use with Codex MRLVDs should only be recommended for use after it can be demonstrated that the method(s) will meet established performance characteristics or provide an improvement to current methods, regulatory decision making and regulatory consistency.

The developer of the method must determine: (a) the analytical response obtained when the matrix is known to be free from chemical interferences; (b) the method variability, and (c) the lowest concentration at which the amount of analyte present can be detected with reasonable statistical certainty. The data should demonstrate that the proposed method can satisfactorily recover and identify known amounts of the analyte that have been added to the test sample. Finally, the developer should demonstrate that the proposed method can satisfactorily recover the analyte from the target tissue matrix in which it has been biologically bound or incurred. Recovery studies must demonstrate absence of responses from substances that may interfere or adversely affect the reliability of the analysis.

The method must demonstrate acceptable method performance in controlled laboratory environments and in field trials which represent anticipated operating conditions, if that is the intended use of the method. The results must be verified by appropriate quality assurance and quality control procedures, including analysis of known blank and positive control samples. Analysis of sufficient numbers of both positive and negative control samples must be performed to establish false positive and false negative rates, with a statistically appropriate number of these samples analyzed by a separate method to verify the results.

A complete description of the method must be provided which includes the scientific principle(s) upon which the method is based, preparation of analytical standards, appropriate tissues the method is suitable for, shelf-life and storage conditions for the analyte in solution and in the target tissue matrix, reagent and standard shelf-life stability, instrumentation as well as their performance

standards and calibration procedures, and identification of critical steps and stopping places. Test limitations as well as appropriate and inappropriate uses of the test must be described. Critical test components and reagents must be identified and specifications described. The developer must provide procedures for demonstrating evidence of satisfactory method performance as well as guarantee the long term availability of all components necessary to successfully perform the test.

For rapid test procedures, the quality control criteria needed to verify and maintain acceptable method performance and to determine that a test kit is operating properly must be provided. Information to verify proper test data interpretation associated with the quality control criteria must be specified. A standard curve prepared for the analyte of interest of known purity is needed. A typical analytical curve prepared by fortifying blank test material with the analyte of interest must be provided.

Data from uncontaminated, fortified, and dosed test material is required to show that the method meets the specificity, precision, systematic error, and accuracy attributes for its intended use. Test samples should be fortified at 0.5 (where practical), 1 and 2 times the MRLVD. Additional samples within these concentration limits may be included.

Data from inter-laboratory studies should be provided on the analytical worksheet developed for evaluating methods for Codex MRLVDs. The method should be tested in three or more laboratories for ease in evaluating multi-laboratory study reports. Each laboratory should analyze samples fortified as stated previously and should test biologically incurred samples containing the analyte at the same concentrations.

Test kits should utilize simple, unambiguous procedures. The analytical procedures designed into test kits to be used by field personnel should be successfully evaluated by at least ten trained individuals in a properly designed study before being placed into general use. The study environment must be similar to that expected for routine use of the test. The design should provide sufficient data for a statistical description of false positive and false negatives, and allow determination of the analytical limits of the test. Participants should include those individuals who have been trained by the developer of the test to determine that training procedures are sufficient to provide acceptable method performance.

STANDARD REFERENCE MATERIALS FOR VETERINARY DRUG RESIDUE ANALYSIS

At the present time it is usually not practical to develop standard reference materials for determination of residues of veterinary drugs in foods. There are specific difficulties in developing standard reference materials for international use as noted below.

Some drugs are not sufficiently stable in test materials at ordinary freezer temperatures. Veterinary drug residue concentrations commonly deplete with time, dependent upon the analyte and test material, at ordinary freezer temperatures. These test materials must be stored and shipped at ultra-cold temperatures or use lyophilized, irradiated, or treated otherwise to reduce enzymatic activity and prevent loss of analyte. The relevant studies for most compounds of interest to CCRVDF have not been published at this time, so it is not known whether treatments noted above will affect the extent to which the drugs of interest are bound to the tissues, whether drug residues remain stable in tissues, or whether they might chemically alter the trace residues.

Recognized standard reference materials are generally very expensive and, considering their other limitations, they are generally not cost effective for residue analysis. Commercial reference standards for veterinary drugs have limited availability at the present time. Because of these and other limitations, such as analytical variability of a method versus the concentration of the analyte (i.e., low mg/kg to µg/kg), standard reference materials are generally inappropriate.

ANNEX 11

Melengestrol acetate (CCRVDF chronology)

CCRVDF (session)	Discussion/Status
11th CCRVDF (1998)	Added melengestrol acetate (MGA) to the priority list for evaluation or re-evaluation at the 54th JECFA[27]
12th CCRVDF (2000)	Agreed to not consider the recommendations of the 54th JECFA.[28]
13th CCRVDF (2001)	Advanced the temporary MRL for MGA to Step 5 and noted that MGA was scheduled for re-evaluation by the 58th JECFA for a practical analytical method for monitoring residues at the recommended MRL.[29]
14th CCRVDF (2003)	Decided to retain the MRLs at Step 6 and requested JECFA re-evaluation based on new information and additional data to be submitted.[30]
15th CCRVDF (2006)	Was informed of an inaccuracy in the calculation of the TMDI for MGA and decided to request JECFA to reassess the recommended MRLs from the 62nd JECFA and to circulate for comments at Step 6 the MRLs from the 66th JECFA for consideration at it next session.[31]
16th CCRVDF (2006)	Considered the MRLs for MGA recalculated by the 66th JECFA. However, because of the lack consensus on the further advancement of the MRLs, the Committee agreed to retain the MRLs at Step 7 for further consideration at its next session (scheduled in 2007).[32]

[27] ALINORM 98/31, para 121 and Appendix VIII.
[28] ALINORM01/31, para. 61.
[29] ALINORM 03/31, para 43.
[30] ALINORM 03/31A, paras 48 and 113 and Appendix VII.
[31] ALINORM 05/28/31, paras 61-62.
[32] ALINORM 06/29/31, para. 73, Appendix III.

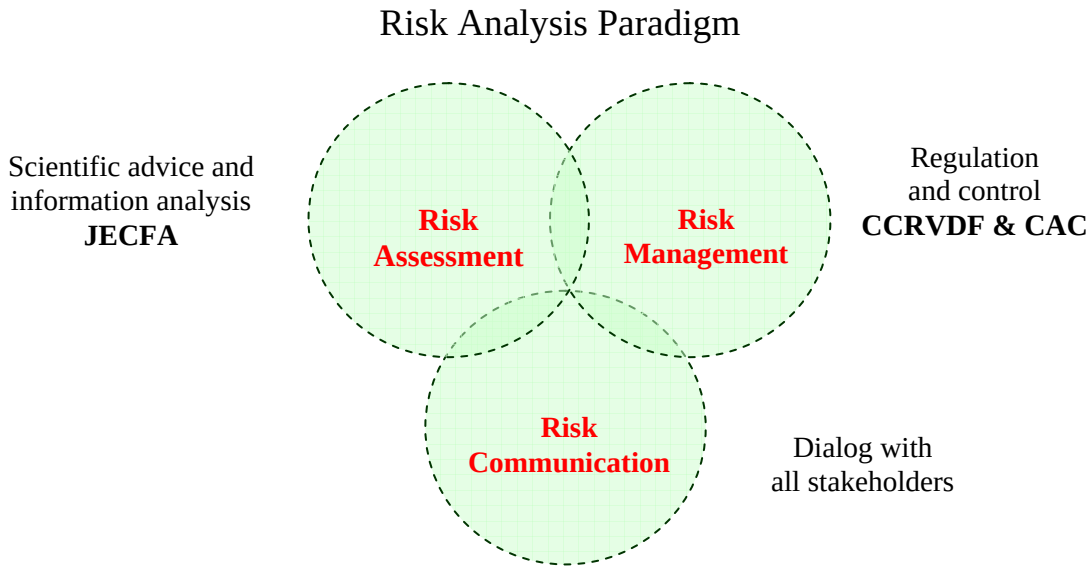
ANNEX E-2

REPLIES OF THE JOINT FAO/WHO JECFA SECRETARIAT TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

Introduction

Risk Analysis is a process consisting of three components: risk assessment, risk management and risk communication. Risk management activities for veterinary drugs within Codex are carried out by the CCRVDF, which prepares draft standards, guidelines and recommendations for consideration by the CAC. Risk assessment activities are performed by JECFA, which is an independent scientific expert body, which advices CCRVDF, but also Members and WHO and FAO directly. JECFA provides independent advice and as such is not part of Codex. Risk communication is the responsibility of all involved parties. JECFA has provided scientific advice on veterinary drug residues since 1982. The separation of tasks is illustrated in the graph below.

Annex 1 gives a brief fact sheet on JECFA, which has been meeting since 1956, i.e. it predates Codex.



3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

The elaboration and application of risk assessment principles are within the responsibility of the scientific expert bodies. Codex bodies elaborate risk assessment policies as they relate to their respective areas of work for the risk assessment bodies in terms of the respective roles and tasks and general guidance on the type of scientific advice requested.

The following lists the key international risk assessment documents relevant to the assessment of veterinary drug residues in food:

– The basis for JECFA risk assessments of veterinary drug residues in food: Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food, World Health Organization, Geneva 1987. http://www.inchem.org/documents/ehc/ehc/ehc70.htm. Subsequently, these principles have been further elaborated, clarified and updated in JECFA meetings dealing with veterinary drug residues in food. These agreed updates are reported under 'General Considerations' in each report. This is a continuing effort to have up-to-date risk assessment principles and methods applied. These principles have been developed over the years of evaluation of different chemical substances, including veterinary drugs.

– Consolidation of all these principles and harmonization between the assessment of veterinary drug residue and pesticide residue, to the extent useful, within the 'Project to update the principles and methods for the assessment of chemicals in food', to be published by the end of 2006. http://www.who.int/ipcs/food/principles/en/

– Principles and methods for the derivation of maximum residue limits of veterinary drugs in food as elaborated by JECFA have been compiled in a format easily accessible to the public in the following document: Procedure for recommending maximum residue limits – residues of veterinary drugs (2000) ftp://ftp.fao.org/es/esn/jecfa/2000-06-30_JECFA_Procedures_MRLVD.pdf

– The data requirements for the assessment of the residues of veterinary drugs have been detailed by the Committee at the 32nd (1987) and 42nd (1994) meetings. These are contained in the above publication. Furthermore, a more complete description of these procedures is available from a recent expert FAO/WHO/RIVM workshop on the update of principles and methods of risk assessment: Maximum Residue Limits (MRLs) for pesticides and veterinary drugs (report available at the following website ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf).

– Several other documents regarding various aspects for the risk assessment of chemicals as developed and published by the International Program on Chemical Safety, in particular (but not exclusively):

- Guidance values for health-based exposure limits. Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits (EHC No 170, 1994) http://www.inchem.org/documents/ehc/ehc/ehc170.htm
- Biomarkers In Risk Assessment: Validity And Validation, Environmental Health Criteria 222, 2001. http://www.inchem.org/documents/ehc/ehc/ehc222.htm
- IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis. Regulatory Toxicology and Pharmacology Volume 34 (2001) 146-152. http://www.who.int/ipcs/publications/methods/harmonization/en/index.html
- Harmonization Project Document No. 2, Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment, WHO, Geneva 2005. http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf
- Guidance on acute reference dose setting. Food and Chemical Toxicology 43 (2005) 1569–1593 http://www.who.int/ipcs/food/jmpr/arfd_guidance.pdf

All these documents are the outcome of international expert meetings and represent the agreed views of the participating experts and several of those have also been published in the scientific literature. There is a continuous effort to update and harmonize on an international level risk assessment methodologies for chemicals.

4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

As outlined under question 3 above, the elaboration and application of risk assessment principles are within the responsibility of the scientific expert bodies. Regarding the principles for the risk assessment of chemicals in food, including of veterinary drug residues in food, please refer to the list of international risk assessment guideline documents above.

6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

Risk assessment comprises of four steps, as defined by many national and international bodies:

Hazard identification: identification of potential adverse health effects as inherent property of a compound.

Hazard characterization: includes dose-response assessment, considerations on species sensitivity, relevance of specific effect for humans etc.

Exposure assessment: estimation of dietary intake

Risk Characterization: integration of the hazard characterization and exposure assessment for a qualitative or quantitative estimate of risk.

Main reference: Application of risk analysis to food standards issues: report of the Joint FAO/WHO Expert Consultation, 1995.

7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? [see Canada's comments in para. 72 of its Rebuttal Submission]

There are no risk assessment guidelines available from the Codex Alimentarius Commission, which applies to the assessment principles and procedures of JECFA. JECFA is an expert committee which has been called into existence by the Director Generals of FAO and WHO. The constitutions and rules of both organizations for such committees are in particular considered in Article VI of the Constitution of FAO and the Regulations for Expert Advisory Panels and Committees of WHO lay down the basic rules which assure excellence and independence of expert committees which provide scientific advice to both organizations.

Throughout its existence JECFA has continued to develop principles for the safety assessment of chemicals in food (see answer to question 3 above).

In general, most risk assessments of chemicals today on a national and international level are deterministic, i.e. they use a point estimate for the toxicological endpoint and a point estimate for the exposure assessment. This is not considered a limitation of the risk assessment process, but often a necessity due to the information at hand. Uncertainties around these point estimates should be considered in the risk assessment process. The current risk assessment process, which includes consideration of sensitive subpopulations, is considered to be sufficiently conservative to be public health protective.

Increasing efforts are under way, also within the International Program on Chemical Safety, to explore methods to perform probabilistic risk assessment, i.e. include distributions rather than point estimates in the risk assessment process. In the area of exposure assessment probabilistic methods have been developed and are increasingly applied, also by JECFA, however probabilistic methods in the toxicological assessment are not yet internationally agreed and are not yet commonly applied. Moreover, the outcome of a probabilistic risk assessment is much more difficult to interpret and apply by risk managers.

Probabilistic or deterministic approaches can be applied, independent if a compound is assumed to act via a threshold mechanism, i.e. non-linear, or not. JECFA's assessment process is based on the mechanism of action of the compound to be evaluated, non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect. In such a case, as for the hormones, a no-effect-level can be determined from which an ADI can be established.

JECFA has in its reports and in the toxicological monographs on the safety assessment of the hormones used risk assessment principles particularly targeted to the evaluation of such substances. JECFA has distinguished between hormones that are identical to those occurring naturally in food-producing animals and human beings, i.e. endogenously produced hormones and substances with hormonal activity, which are either synthetic or naturally occurring but which are not identical with human endogenous hormones. As is standard practice, all toxicological effects of the hormones have been considered by JECFA in the risk assessment, including the hormonal no-effect-levels (the dose at which no effects are found) and other relevant toxicological end-points, such as reproductive toxicity, genotoxicity and potential carcinogenicity. The conclusion of the risk assessments are detailed in the respective report and monographs of JECFA.

8. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

Dose-response assessment is an integral part of each assessment and is an essential part of the hazard characterization step. This can be done in a quantitative or a qualitative way. In the qualitative sense this is the determination of a no-effect-level (NOEL or NOAEL) from an experimental or epidemiological study. For the hormones JECFA used this approach. In some cases, for contaminants (e.g. aflatoxins), JECFA has applied a quantitative dose-response assessment.

The International Programme on Chemical Safety (IPCS) has recently held an international workshop to further elaborate the principles of dose-response assessment. The final report will be published in the Environmental Health Criteria Series: Principles for Modelling Dose-Response for the Risk Assessment of Chemicals. Specifically as relevant to chemicals in food, part of the report will also be included in the updated principles document on the risk assessment of chemicals in food (see under question 3). The draft report was made available for public comment, and is accessible under: http://www.who.int/ipcs/methods/harmonization/draft_document_for_comment.pdf

9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

ADI: acceptable daily intake: An estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk (standard human = 60 kg). The ADI is listed in units of mg per kg of body weight.
Source: JECFA glossary of terms: http://www.who.int/ipcs/food/jecfa/glossary.pdf (based on EHC 70)

ADI: Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk.
Related terms: *Reference dose, Tolerable daily intake*
Source: IPCS Risk Assessment Terminology
http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

MRL: Residues of veterinary drugs is defined as follows in the Procedural Manual of the Codex Alimentarius Commission: Residues of veterinary drugs include Parent compounds and/or their metabolites in any edible portion of the animal product, including associated impurities of the veterinary drug concerned, which may be of significance to human health. On a recommendation to harmonize the definitions of residues of veterinary drugs and pesticides from the conclusions of the FAO/WHO workshop on updating the principles and methods of risk assessment: MRLs for pesticides and veterinary drugs (see answer to question 3 above), a modified definition was adopted by the 66th meeting of JECFA as follows: Parent compounds and/or their metabolites, including associated impurities of the veterinary drug concerned, in any edible portion of the animal product, which may be of significance to human health.

10. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please also identify and describe any steps that are taken in the risk assessment process to build a margin of safety into to the final recommendation.

Establishment of ADI

Source: EHC 70:

> 5.5. Setting the ADI
>
> Almost any substance at a high enough test level will produce some adverse effect in animals. Evaluation of safety requires that this potential adverse effect be identified and that adequate toxicological data be available to determine the level at which human exposure to the substance can be considered safe.
>
> At the time of its first meeting, JECFA recognized that the amount of an additive used in food should be established with due attention to "an adequate margin of safety to reduce to a minimum any hazard to health in all groups of consumers" (9, pp. 14-15). The second JECFA, in outlining procedures for the testing of intentional food additives to establish their safety for use, concluded that the results of animal studies can be extrapolated to man, and that
>
> > "some margin of safety is desirable to allow for any species difference in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease

processes in the human population, the difficulty of estimating the human intake, and the possibility of synergistic action among food additives" (10, p. 17).

This conclusion formed the basis for establishing the "acceptable daily intake", or ADI, which is the end-point of JECFA evaluations for intentional food additives. In the context in which JECFA uses it, the ADI is defined as an estimate (by JECFA) of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

The ADI is expressed in a range, from 0 to an upper limit, which is considered to be the zone of acceptability of the substance. JECFA expresses the ADI in this way to emphasize that the acceptable level it establishes is an upper limit and to encourage the lowest levels of use that are technologically feasible.

Substances that accumulate in the body are not suitable for use as food additives (39, p. 8). Therefore, ADIs are established only for those compounds that are substantially cleared from the body within 24 h. Data packages should include metabolism and excretion studies designed to provide information on the cumulative properties of food additives.

JECFA generally sets the ADI of a food additive on the basis of the highest no-observed-effect level in animal studies. In calculating the ADI, a "safety factor" is applied to the no-observed-effect level to provide a conservative margin of safety on account of the inherent uncertainties in extrapolating animal toxicity data to potential effects in the human being and for variation within the human species. When results from two or more animal studies are available, the ADI is based on the most sensitive animal species, i.e., the species that displayed the toxic effect at the lowest dose, unless metabolic or pharmaco-kinetic data are available establishing that the test in the other species is more appropriate for man (section 5.5.1).

Generally, the ADI is established on the basis of toxicological information and provides a useful assessment of safety without the need for data on intended or actual use and consumption. However, in setting ADIs, an attempt is made to take account of special subpopulations that may be exposed. Therefore, general information about exposure patterns should be known at the time of the safety assessment (section 5.5.6). For example, if a food additive is to be used in infant formulae, the safety assessment is not complete without looking carefully at safety studies involving exposure to very young animals.

JECFA uses the risk assessment process when setting the ADI, i.e. the level of "no apparent risk" is set on the basis of quantitative extrapolation from animal data to human beings.

The above described procedure and principles are equally applied to residues of veterinary drugs by JECFA.

Establishment of the ADI follows the following steps:

– determination of a no-observed-effect level

– application of safety factors

A safety factor has been used by JECFA since its inception. It is intended to provide an adequate margin of safety for the consumer by assuming that the human being is 10 times more sensitive than the test animal and that the difference of sensitivity within the human population is in a 10-fold range.

In determining an ADI, a safety factor is applied to the no-observed-effect level determined in an appropriate animal study.

JECFA traditionally uses a safety factor of 100 (10 x 10) in setting ADIs based on long-term animal studies, i.e., the no-observed-effect level is divided by 100 to calculate the ADI.

Deviation from the default safety factor can be considered when e.g. the inadequacy of database may justify a larger safety factor, or when a no-observed effect level is derived from adequate human data a smaller safety factor may be applied. Moreover, recently the concept of chemical specific adjustment factors (CSAF) has been applied if appropriate data were available. (Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment, WHO, Geneva 2005. http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf)

Residue evaluation:

Derivation and recommendation of maximum residue limits (MRLs)

JECFA has specified the data requirements that are intended to adequately identify and characterize the veterinary drug being evaluated for toxicology and residue considerations. Specific information is requested on mode of administration, dose and formulation, pharmacokinetic, metabolic and pharmacodynamic studies, residue depletion studies with radiolabelled drug and non-radiolabelled drug in target animals at appropriate times of withdrawal, information on major residue components for determining a marker residue and target tissue. In addition, information is requested regarding free and bound residues (including bioavailability), routine analytical methods and appropriate method performance factors and information on antimicrobial assays for those compounds for MRL considerations on antimicrobial end points. The above data are requested for all relevant food animal species and tissues, as well as milk, eggs and honey using good veterinary practice. The JECFA has developed a mathematical model to account for bound residues in tissue. In consideration of MRLs, the JECFA also reviews the comparative metabolism between laboratory animals and food animals to determine qualitative or quantitative similarities or differences in metabolites across species.

The JECFA does not recommend MRLs when the theoretical maximum daily intake (TMDI) of residues substantially exceeds the ADI. The TMDI is the upper limit consideration in recommending MRLs. For purposes of recommending MRLs, the JECFA uses a theoretical food basket that consists of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 1500 g milk, 100 g for eggs and 20 g for honey. Considerations in MRLs are based on the adequacy of the data. Where a large database is available, statistical approaches to MRLs may be used.

JECFA uses radiolabelled parent drug studies in intended host animal species as well as additional studies with non-radiolabelled parent drug for recommending MRLs and a marker residue compound and appropriate target tissues for residue analysis. Dose treatments preferably considered are those conducted at the maximum approved dose. Residues are generally determined in all four edible tissues – muscle, liver, kidney and fat as well as milk and eggs, where the data are sufficient. JECFA identifies the appropriate stable compound that can be used as the marker residue and indicates the most appropriate tissues for analysis, considering needs of national authorities for domestic residue control programs and product intended for international trade. These studies also provide the necessary information to determine consideration of bound residues and relationships between the marker residue and total residues of concern as determined by the ADI.

JECFA has recognized that the use of veterinary drugs in food producing animals can result in residues that are neither extractable from tissue nor readily characterized using mild extraction procedures. The Committee has developed a procedure to estimate the maximum daily intake of

residues of a drug that has a bound residue component. It takes into account the toxicological potency and bioavailability of the residues.

Residues = Free residues + Bioavailable bound residues.
Bound residue = Total residue - (extractable fraction + endogenous fraction).

$$\text{Residues} = P_0 + \sum_{n=n_1}^{n_x} (M_n \times A_n) + (\text{Bound residue} \times \text{fraction bioavailable} \times A_b) \quad \ldots\ldots (1)$$

where

P_0 = amount of parent drug per kg of tissue.
$n_1..n_x$ = different metabolites of the parent drug.
M_n = amount of (unbound) parent drug metabolite n per kg of tissue.
A_n = toxicological potency of n relative to that of parent drug.
A_b = estimated relative toxicological potency of the metabolites in the bound residue (when no information is available, use $A_b = 1$)

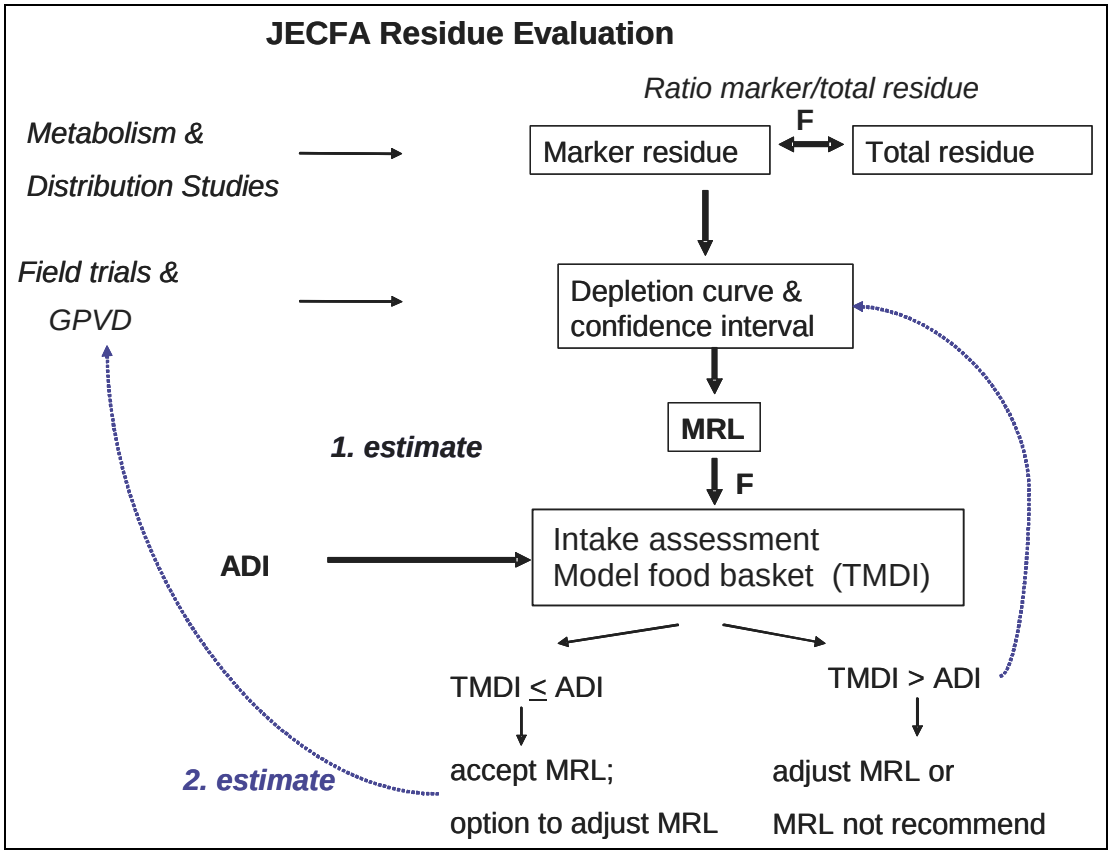
JECFA considers that in the absence of other data, a bound residue should be considered of no greater toxicological concern than the compound for which the ADI was established. In considering the safety of bound residues, JECFA acknowledges that a suitable extractable residue analyte may be selected as a marker compound and used for recommending an MRL if bound residues make up an insignificant portion of the total residue. Where bound residues become a significant portion of the total residues of toxicological significance, then the procedure described may be used to assess their safety. The use of residue data for the purpose of safety assessment is evaluated on a case-by-case basis.

JECFA make final recommendations for MRLs of a veterinary drug in appropriate food animal species and tissues when there are adequate data and compatible with the ADI. Temporary MRLs may be recommended when there is a full ADI yet adequate residue or method performance data are lacking or when the ADI is temporary. The Committee may recommend MRLs "not specified" or "unnecessary" when there is a wide margin of safety of residues when compared with the ADI). Finally, JECFA may determine that MRLs cannot be recommended because of significant deficiencies in either residue data or available analytical methods or when an ADI is not established.

JECFA has devoted a significant effort to analytical methods performance because of the strong role it has in recommending MRLs. JECFA has developed analytical methods performance factors for consideration as suitable for determining compliance with a recommended MRL. Major considerations include accuracy (recovery), precision, reproducibility, sensitivity (dose-response), and selectivity, among others. Use of common laboratory instruments and solvents that do not have environmental or health considerations are important factors. Guidance for analytical method performance factors has been described in individual reports. Methods are considered in cooperation with the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) *ad hoc* Working Group on Methods of Analysis and Sampling.

JECFA has devoted efforts recently to develop statistical tools for data analysis to derive MRLs. A JECFA paper has been prepared as well as a set of proposed statistical tools for JECFA experts to apply for recommending a set of MRLs. The approach has to meet two specific criteria: 1) the time point selected to recommend the MRLs is compatible with registered uses (Good Practice in the Use of Veterinary Drugs), and 2) that it does not result in a theoretical residue exposure in excess of the ADI.

A summary of the JECFA procedures for recommending MRLs is described below.



The MRL recommendation procedure is an iterative process. The MRL is not derived directly from the ADI. If the ADI is based on toxicological end-points, all residues of toxicological relevance are considered, if the ADI is based on microbiological end-points, all residues of microbiological relevance are considered. The MRL recommendation procedure also takes into account the conditions of use (e.g. use of the veterinary drug according to good practice in the use of veterinary drugs GPVD) and the residues that result from such use (e.g. residue depletion studies). It also considers results of radiolabel residue studies, the bioavailability of bound residues, the identification of target tissues and a marker residue, the availability of practical analytical methods, estimated exposure resulting from recommended MRLs and consideration of extension of the MRLs to tissues, eggs and milk of other species.

The initial consideration in recommending an MRL is whether it is sufficiently protective of human health. If the use of the veterinary drug yields an estimated intake of veterinary drug residues consistent with the ADI, the recommended MRLs may then be adjusted accordingly when taking into account the other factors noted above. As a general principle, the Committee will not normally recommend an MRL that results in residue levels that lead to dietary intake exceeding the ADI based on toxicological or microbiological considerations.

11. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

If there are substantial data gaps and important information missing, JECFA can not establish an ADI. However, JECFA can allocate a temporary ADI when data are sufficient to conclude that use of the

substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. A higher-than-normal safety factor is used when establishing a temporary ADI and an expiration date is established by which time appropriate data to resolve the safety issue should be submitted to JECFA. The temporary ADI is listed in units of mg per kg of body weight. Source: JECFA glossary of terms: http://www.who.int/ipcs/food/jecfa/glossary.pdf

12. In paras. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

JECFA is the risk assessment body and only considers health impact of specific risk management options when specifically requested by CCRVDF, e.g. JECFA could estimate the impact on exposure of different MRLs, if asked to do so. Consideration of risk management options is in the responsibility of the risk management body, hence CCRVDF.

13. With respect to the data used in the evaluation of chemical substances, such as the hormones at issue, what are the data requirements for JECFA's work and how are they determined? Who provides data for such evaluations? Are any records/archives kept by JECFA? Do any confidentiality rules apply to data submitted to JECFA or should all data be publicly available? If confidentiality rules apply, in which circumstances? [see paras. 95-96 of EC Rebuttal Submission (US case), paras. 78-79 of EC Rebuttal Submission (Canada case), para. 123 of Canada Rebuttal Submission]

Data requirements:

In the public call for data for submission to the Joint FAO/WHO JECFA Secretariat that precedes each JECFA meeting, governments, interested organizations, producers of these chemicals, and individuals are invited to submit data relating to the compounds listed in agenda. The data requirements are detailed in the call for data and include the following:

Data relevant to the evaluation of veterinary drug residues in food products of animal origin, including:

1. chemical identity and properties of the drug;

2. its use and dosage range;

3. pharmacokinetic, metabolic, and pharmacodynamic studies in experimental and food-producing animals, and in humans when available;

4. short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity and developmental toxicity studies in experimental animals and genotoxicity studies;

5. special studies designed to investigate specific effects, such as those on mechanisms of toxicity, no-hormonal-effect levels, immune responses, or macromolecular binding;

6. for compounds with antimicrobial activity, studies designed to evaluate the possibility that residues of the compound might have an adverse effect on the microbial ecology of the human intestinal tract; and

7. studies providing relevant data on the use of and exposure to the drug by humans, including studies of effects observed after occupational exposure and epidemiological data following clinical use in humans

8. pharmacokinetic and metabolic studies in experimental animals, target animals, and humans when available (information required by both FAO and WHO);

9. residue-depletion studies with radiolabelled drug in target animals from zero withdrawal time to periods extending beyond the recommended withdrawal time (these studies should provide information on total residues, including free and bound residues, and major residue components to permit selection of a marker residue and target tissue);

10. residue-depletion studies with unlabelled drug for the analysis of marker residue in target animals and in eggs, milk, and honey (these should include studies with appropriate formulations, routes of application, and species, at doses up to the maximum recommended);

11. a description of the analytical procedures used by the sponsor for the detection and determination of parent drug residues with information on validation and performance characteristics; and

12. a review of routine analytical methods that may be used by regulatory authorities for the detection of residues in target tissue, including information on quality assurance systems and sampling procedures recommended.

Additional information can be found in the procedural guidelines for JECFA:

Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives: Residues of veterinary drugs in food, Geneva, August 1996 http://www.who.int/ipcs/food/jecfa/en/guidelines_vet_drugs.pdf and ftp://ftp.fao.org/es/esn/jecfa/2000-06-30_JECFA_Procedures_MRLVD.pdf

In the particular case of the hormones, JECFA also detailed in the respective report, the additional data needed to perform a complete risk assessment of the individual hormones under review.

Data submissions:

Data are mainly provided by companies who produce the compounds, additional data are sometimes provided by national authorities, such as data on levels analyzed in foods.

Records and archives – confidentiality rules:

The submitted data may be published or unpublished and should contain detailed reports of laboratory studies, including individual animal data. Reference should be made to related published studies, where applicable. Summaries in the form of monographs are helpful, but they are not in themselves sufficient for evaluation. Unpublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA. Neither FAO nor WHO have facilities for storing printed data for long periods of time, so confidential data will either be returned to the submitter at the submitter's expense or destroyed after the evaluations have been completed. Key material can be stored up to five years and will then be destroyed.

Public accessibility of JECFA assessments:

It is important to note that JECFA evaluations are completely publicly available, and a detailed description of the data evaluated is accessible through the monographs. Specific information regarding the manufacturing process of substances, which are considered confidential for commercial purposes may be excluded from the reports and monographs, if agreed by the Joint FAO/WHO Secretariat.

Short explanation of JECFA publications:

– WHO Technical Report Series (TRS) These reports, published by the World Health Organization, contain concise toxicological evaluations and the chemical and analytical aspects of each substance reviewed by JECFA, as well as information on the intake assessment. Reports reflect the agreed view of the Committee as a whole and describe the basis for their conclusions.

– WHO Food Additive Series (FAS) These monographs, published by the World Health Organization, contain detailed descriptions of the biological and toxicological data considered in the evaluation, as well as the intake assessment, including detailed literature references.

– Compendium of FAO Veterinary Drug Residue Monographs These monographs, published by the Food and Agriculture Organization, contain the data and the evaluations used to recommend MRLs for veterinary drug residues. They were originally published as the FAO Nutrition Meetings Report Series, and later as FAO Food and Nutrition Papers. The information from these publications has been updated and compiled into FAO Food and Nutrition Paper 41. Individual, fully updated evaluations are also available here in a combined online compendium, searchable by both drug name and functional class. New monographs will be published in the FAO JECFA Monograph series from 2006 onwards.

14. How are experts involved in JECFA's work selected? What are the selection criteria?

Detailed procedures are outlined in the procedural guidelines:
WHO procedural guidelines for JECFA:
http://www.who.int/ipcs/food/jecfa/procedural_guidelines%20_drugs.pdf

FAO procedural guidelines for JECFA:
ftp://ftp.fao.org/es/esn/jecfa/2002-09-24_Vet_Drugs_Proc_Guidelinesb.pdf

Guideline for selection of experts to serve on the roster of JECFA: These guidelines are governed by Procedural rules of FAO and WHO (see response to question 7, first paragraph). Article VI (sections 2, 3 and 7) of the Constitution of FAO and the Regulations for Expert Advisory Panels and Committees of WHO lay down the basic rules of JECFA. All members and associated drafting experts of JECFA act strictly in their own capacity. Declarations of interest are signed by each expert in advance of the meeting and considered by the Joint FAO/WHO JECFA Secretariat.

JECFA is not a standing committee, the selection of members for each meeting is made after a careful consideration of the scientific credentials of the various candidates, and a balance of scientific expertise and other experience that is considered essential considering the items on the agenda of the meeting. The selection process respects as well FAO and WHO policies on regional representation and gender balance. FAO and WHO meet the costs of experts' attendance at JECFA meetings. Being a joint committee of FAO and WHO, the organizational framework of JECFA complies with the rules of both organizations. The selection process for experts is undertaken in mutual consultation by the Joint Secretariats. When calling for and selecting experts, FAO and WHO assure that selections

complement each other. Both organizations establish listings of experts, called rosters; appointments are for a period of five years. Experts are selected from those rosters for each meeting, in which capacity they either attend the meeting as members or assist the Secretariat with preparatory work before the meeting and usually participate in the meeting itself. Each member invited by WHO must also be a member of a WHO Food Safety Advisory Panel and is appointed by the Director General of WHO. Invitations to each meeting by FAO is decided by the Director General of FAO.

17. Is the table in Exhibit CDA-32 outlining the chronology of JECFA's assessment of the hormones at issue and the resulting documentation complete?

The document describes the published documentation relating to the risk assessment of the individual hormones, reports and monographs, adopted by JECFA and published by WHO and FAO. The list is complete (in some instances page numbers are given only as the first page and in other as the page numbers of entire section in question), with the exception of the summary and conclusions of the 66th JECFA meeting held 20 - 28 February, 2006 (page 3). In this meeting, the Committee further deliberated on the MRLs previously proposed for melengestrol acetate, at the request of CCRVDF (ftp://ftp.fao.org/ag/agn/jecfa/jecfa66_final.pdf.

18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

In general, there is a clear procedure for placing compounds on the agenda of JECFA to perform or update a risk assessment. If new scientific data become available that may impact on an existing risk assessment, there are several possibilities for a compound to be scheduled for re-evaluation by JECFA.

Requests for the evaluation of certain veterinary drugs and consideration of issues of a general nature by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) may come from a number of sources:

1. Codex committees

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) refers substances to JECFA based on priorities that it establishes using criteria that it has developed that are in accord with accepted procedures of the Codex Alimentarius Commission.

2. FAO and WHO Member States

FAO and WHO Member States may request the inclusion of veterinary drugs on the agenda of JECFA through a direct request to the FAO and WHO Secretariats. Such a request must be accompanied by a commitment to provide the necessary data 6-7 months before the meeting.

3. Sponsors

For veterinary drugs not previously evaluated by JECFA, an industry sponsor may forward a request for evaluation through the government of a Member State to CCRVDF, with a commitment to provide the relevant data. Requests for the re-evaluation of a veterinary drug that has been reviewed by JECFA previously may be forwarded directly to the JECFA Secretariat. As with all other substances on the agenda, the Joint Secretariat includes the substance in the call for data for the meeting to ensure that all interested parties have the opportunity to submit data.

4. JECFA Secretariat

The JECFA secretariat may place a veterinary drug on the agenda for re-evaluation even though no outside request has been received.

5. JECFA itself

The Committee often establishes a temporary ADI or recommends temporary MRLs, with a request for further data by a certain time. These veterinary drugs, which have the highest priority for evaluation, are placed on the agenda of the appropriate meeting by the Joint Secretariat.

Source: WHO procedural guidelines for JECFA, Annex 1:
http://www.who.int/ipcs/food/jecfa/procedural_guidelines%20_drugs.pdf

19. What would be the procedures for requesting JECFA to re-evaluate its recommendations in light of new concerns/evidence? How would an amendment be adopted? Has the European Communities approached JECFA for this purpose with respect to the hormones at issue in this case? [see Exhibit EC-63]

Regarding the procedures for a compound to be re-evaluated please refer to the response under question 18 above.

The re-evaluations of compounds follow the same procedure as an evaluation performed for the first time, with clear identification of the new data that were assessed. Data from previous assessments relevant for the evaluation are also described, and the final assessment published in the report and if relevant also as a monograph addendum. JECFA reports are adopted before the close of the meeting, i.e. the final report for each meeting, including the general considerations as well as the assessments for all compounds on the agenda, are adopted at the meeting before it is adjourned. After that only editorial changes are made.

European Union has not asked the JECFA Secretariat to bring their data referred to in the report of the 11th session of CCRVDF (see below point 1 of question 20) before JECFA for review. The studies referred were finalised later than the 52nd JECFA meeting and the Secretariat has not scheduled these substances on the agenda of JECFA since that meeting.

20. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by CCRVDF? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

(1) What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999?

The natural hormones were placed on the agenda for re-evaluation by the JECFA secretariat, as documented in the report of the 11th Session of CCRVDF:

From the report of the 11th Session of CCRVDF, ALINORM99/31:

125. The question was raised as to why the natural hormones (estradiol-17b, progesterone, and testosterone) had been placed on the agenda of the JECFA for reevaluation. It was pointed out that they were placed on the agenda at the initiative of the JECFA Secretariat to ensure that all the latest information had been evaluated. On the evaluation of natural hormones, the European Commission pointed out that it had written to the JECFA Secretariat in order to make JECFA aware that a number of substantial studies were currently being prepared by the EU and had requested that the JECFA evaluation be deferred to a later JECFA meeting. The European Community therefore reiterated the request to defer the JECFA consideration.

ALINORM 99/31
APPENDIX VIII

PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR REEVALUATION

1. Substances scheduled for evaluation or reevaluation at the fifty-second meeting of JECFA in February 1999:

Substances on the previous priority list of CCRVDF	**Substances recommended for reevaluation by JECFA (temporary ADI and/or MRLs) or by the JECFA Secretariat**
Deltamethrin (residues) – toxicological evaluation by 2000 JMPR Permethrin (residues) – toxicological evaluation by 1999 JMPR Phoxim Porcine somatotropin Carazolol	Abamectin (residues; referral from JMPR) Azaperone (analytical method) Dihydrostreptomycin/streptomycin (residues) Doramectin (residues) Natural hormones (estradiol-17β, progesterone, and testosterone) Thiamphenicol

JECFA can decide to reevaluate previous assessment when the Committee is made aware that there is new data which may be pertinent to the risk assessment of the substances in question. The European Union had claimed in the 1997 WTO hormone dispute that new evidence showed that oestradiol-17ß is a directly acting genotoxic carcinogen. Also for the other substances a substantial amount of new studies had been published since the 32nd meeting. Also the 32nd Meeting produced no toxicological monograph for the three nature-identical hormones. The toxicological/endocrinological/ epidemiological data for the 52nd Meeting were retrieved by means of an exhaustive literature survey.

(2) Were the residues data used for the three natural hormones in 1999 the same as those used in 1988?

In the 1988 evaluation, the data has been described in FAO Food and Nutrition Paper 41/1 (1988). In the 1999 evaluation, new information for the three natural hormones was provided, including the complete dossier submitted to the US Food and Drug Administration. FDA kindly permitted the FAO expert to the Committee to search all their relevant files for data. A more complete and transparent assessment of all data, including statistical evaluation, was made (FAO Food and Nutrition Paper 42/12, 2000, p. 37-90). Most of the studies were the same. However, a few additional investigational studies were also reviewed. JECFA also performed a more detailed thorough review of the validity of the analytical methods used in the studies and used only data generated using valid methods. It also performed more detailed statistical and graphical analyses of the data. Since the FAO FNP 41/12

monograph provides all raw data used (in graphical form) and all the calculations performed, the document is also more transparent than the corresponding monograph produced by the 32nd Meeting.

(3) What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988?

From the report of the 52nd JECFA meeting, TRS 893:

Estradiol-17β, progesterone and testosterone were re-evaluated at the present meeting to take into consideration any data that had been generate since their previous review and to make a quantitative estimate of the amounts that could be consumed safely.

Toxicological data

Estradiol-17β. The Committee considered published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of exogenous estrogens. Numerous reports on studies of the use of exogenous estrogens in women were considered, as were studies in experimental animals on the mechanism of action of estradiol-17β. The extensive database derived from the results of epidemiological studies in women taking oral contraceptive preparations containing estrogens or postmenopausal estrogen replacement therapy was also used to evaluate the safety of estradiol-17β.

Progesterone. The Committee considered published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of progesterone. Numerous reports of studies on progesterone in humans were considered. In addition, the extensive database derived from women taking progesterone as a component of oral contraception, as injectable progestogen-only contraception, and in postmenopausal hormone replacement therapy was used to support the safety evaluation.

Testosterone. The Committee considered published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of testosterone. Reports of studies on testosterone in humans were also considered.

Residue studies for the three hormones. Please see answer to point 2 above.

(4) How did the conclusions differ?

Estradiol-17β

Estradiol was reviewed previously by the Committee, at its thirty-second meeting (1988), when it concluded that the establishment of an acceptable residue level and an ADI was 'unnecessary', based on the conclusion that this is a hormone that is produced endogenously in human beings and shows great variation in level according to age and sex. This conclusion was based on studies of the patterns of use of estradiol for growth promotion in cattle, the residues in animals, analytical methods, toxicological data from studies in laboratory animals, and clinical findings in human subjects. The Committee further concluded that estradiol residues resulting from its use for growth promotion in accordance with good husbandry practices were unlikely to be a hazard to humans.

On the basis of its safety assessment of residues of estradiol-17β, and in the view of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level.

At its 52nd meeting in 1999, estradiol-17β was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-50 ng/kg bw on the basis of the NOEL of 0.3 mg/day (equivalent to 5 µg/kg bw per day) in studies of changes in several hormone-dependent parameters in postmenopausal women. A safety factor of 10 was used to account for normal variation among individuals, and an additional factor of 10 was added to protect sensitive populations.

Progesterone

Progesterone was reviewed previously by the Committee, at its thirty-second meeting (1988). The Committee then concluded, that the amount of exogenous progesterone ingested from meat of treated animals would not be capable of exerting hormonal a effect, and therefore any toxic effect, in human beings. The Committee deemed it 'unnecessary' to set an ADI for a hormone that is produced endogenously in human beings and shows marked physiological variation in levels according to age and sex. The Committee concluded that residues arising from the use of progesterone as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health.

On the basis of its safety assessment of residues of progesterone, and in the view of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level.

At its 52nd meeting in 1999, progesterone was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-30 µg/kg bw for progesterone on the basis of the LOEL of 200 mg/day (equivalent to 3.3 mg/kg bw) for changes in the uterus. A safety factor of 100 was used to allow for extrapolation from a LOEL to a NOEL and to account for normal variation among individuals.

Testosterone

Testosterone was reviewed previously by the Committee, at its thirty-second meeting (1988). The Committee the considered an ADI 'unnecessary' for a hormone that is produced endogenously in human beings and shows marked physiological variation in levels according to sex and age. The Committee concluded that residues resulting from the use of testosterone as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health.

On the basis of its safety assessment of residues of testosterone, and in the view of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level.

At its 52nd meeting in 1999, testosterone was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-2 µg/kg bw for testosterone on the basis of the NOEL of 100 mg/day (equivalent to 1.7 mg/kg bw per day) in the study of eunuchs and a safety factor of 1000. The large safety factor was used in order to protect sensitive populations and because of the small number of subjects in the study from which the NOEL was identified.

Conclusions in residues evaluation of all three hormones

The conclusions concerning residues were equivalent in the 1988 evaluation and the 1999 evaluation, but were based on a more detailed discussion. The 52nd JECFA performed a detailed theoretical intake assessment based on a worst case scenario (all animals are slaughtered at the time of the highest hormone levels - this time point differs largely from the time point at which the benefit due to the anabolic effect is greatest). In this assessment intake estimates for preferential meat eaters were performed on the basis of the hormone levels of treated animals in comparison with the corresponding levels in untreated animals and the additional "burden" or "excess intake" was calculated.

For total estrogens the highest excess intakes from approved uses calculated this way were in the order of magnitude of 30-50 ng/person/day. This range of intake is less than 2% of the ADI for estradiol-17β established by JECFA at the 52nd meeting. For certain experimental studies carried out with experimental combinations resulted in an excess intake of around 4% of the ADI.

The highest excess intake of progesterone, the only relevant hormonal active residue from treatment with progesterone, was below 500 ng/person/day for the approved uses of this hormone. This corresponds to 0.003% of the ADI for progesterone established by JECFA.

For testosterone, the highest intake of the free hormone was approximately 60 ng/person/day for all approved uses of this hormone. This represents around 0.2% of the ADI for testosterone established by JECFA.

JECFA also noted that hormone concentrations found in individual populations of treated animals, although they were typically statistically significant higher than untreated controls, were well within the physiological range of these substances in bovine animals. The data assessed and the worst case scenario calculations made indicated a wide margin of safety of consumption of residues from animals treated in accordance with good practice of use of the veterinary drugs containing the hormones in question. JECFA therefore concluded that there was no need to specify numerical maximum residue levels for the three hormones and recommended MRLs not specified in bovine tissues.

(5) What led JECFA to establish ADIs for the three natural hormones?

The additional data reviewed and the need to establish and ADI as quantitative estimate for a safe oral intake. The exposure assessment performed would then allow the comparison of the estimated intake with the ADI. This can mean that maximum residues limits are recommended or if the margin of safety is wide that there is no necessity to derive numerical values.

(6) What are the implications of establishing ADIs?

An ADI is an estimate of a quantity of a substance that can be consumed over life-time without any appreciable health risk, i.e. it is a measure for a safe chronic intake level. The ADI can be used to estimate the safety of proposed maximum residue levels in food and the resulting intake estimates. The ADI can then be compared to actual or estimated intake levels, which are calculated from actual or estimated occurrence data in food times the amount of food consumed. This then leads to conclusions on the safety of the food supply, or of specific foods, including tissues of animal origin. JECFA uses a standard food basket for foods of animal origin, which includes 500 g of meat to be eaten every day of life.

Sufficient new data from observations in humans were available to the 52nd JECFA which were suitable to derive ADIs. The ADI not only provides an estimate of daily intakes which can be

accepted over life time without appreciable health risks, it also enables a quantitative comparison of the excess intakes calculated on the basis of the above mentioned worst case scenario (see point 4 above). The Committee found that the excess intake was in the order of only 0.02 to 4% of the ADI depending on the substance and the product used for the treatment of the animals.

Moreover, the establishment of an ADI implies that there is a threshold of effect for such a compound, below which now toxicological effects occur.

(7) Why were JECFA's more recent recommendations not considered by CCRVDF?

***From 12th CCRVDF report,* ALINORM 01/31**
under report from JECFA: MRLs for estradiol-17β, progesterone and testosterone were recommended as "not specified".

Under MRLs:

Estradiol-17β, Progesterone and Testosterone

84. Recognizing that this Committee had not requested the re-evaluation of these substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, the Committee **decided** not to consider these new recommendations. The MRLs not specified adopted by Codex were the same as those recommended by JECFA at the 52nd meeting.

ANNEX 1

Food and Agriculture Organization of the United Nations

World Health Organization

FACT SHEET - WHAT IS JECFA?
(9 February 2006)

Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food.

To date, JECFA has evaluated more than 1500 food additives, approximately 40 contaminants and naturally occurring toxicants, and residues of approximately 90 veterinary drugs. The Committee has also developed principles for the safety assessment of chemicals in food that are consistent with current thinking on risk assessment and take account of recent developments in toxicology and other relevant scientific areas such as microbiology, biotechnology, exposure assessment, food chemistry including analytical chemistry and assessment of maximum residue limits for veterinary drugs.

JECFA normally meets twice a year with individual agendas covering either (i) food additives, contaminants and naturally occurring toxicants in food or (ii) residues of veterinary drugs in food. The membership of the meetings varies accordingly, with different sets of experts being called on depending on the subject matter.

History and Background

The evaluation of food additives at the international level was initiated as a result of a Joint FAO/WHO Conference on Food Additives held in Geneva, Switzerland in 1955. The Conference recommended to the Directors-General of FAO and WHO that one or more expert committees should be convened to address the technical and administrative aspects of chemical additives and their safety in food. This recommendation provided the basis for the first meeting of JECFA. As of January 2006 the committee has met 65 times and the 67th meeting in June 2006 marks the 50th anniversary of JECFA.

Purpose

JECFA serves as an independent scientific committee which performs risk assessments and provides advice to FAO, WHO and the member countries of both organizations. The requests for scientific advice are for the main part channelled through the Codex Alimentarius Commission (CAC) in their work to develop international food standards and guidelines under the Joint FAO/WHO Food

Standards Programme. The main purposes of this Programme are protecting health of the consumers and ensuring fair trade practices in the food trade. The advice to CAC on food additives, contaminants and naturally occurring toxicants is normally provided to the Codex Committee on Food Additives and Contaminants (CCFAC) and advice on residues of veterinary drugs to the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF).

All countries need to have access to reliable risk assessment of chemicals in food, but not all have the expertise and funds available to carry out separate risk assessments on large numbers of chemicals. JECFA performs a vital role in providing a reliable and independent source of expert advice in the international setting, thus contributing to the setting of standards on a global scale for the health protection of consumers of food and for ensuring fair practices in the trade in safe food. Some countries use information from JECFA in the establishment of national food safety control programmes and CCFAC and CCRVDF develop standards based on evaluations by JECFA.

Under the terms of the Sanitary and Phytosanitary agreement (SPS), scientific, risk based standards established by CAC should be employed in international trade of food. Therefore, governments are likely to request advice from Codex committees, and consequently from JECFA and other international scientific bodies, on the implementation of national standards and legislation related to food safety.

Membership of the Committee

FAO and WHO have complementary functions in selecting experts to serve on the Committee. FAO is responsible for selecting members with chemical expertise for the development of specifications for the identity and purity of food additives, for the assessment of residue levels of veterinary drugs in food, and to assess the quality of the monitoring data. WHO is responsible for selecting members for the toxicological evaluations of the substances under consideration, in order to establish acceptable daily intakes (ADIs), or other relevant guidance values, or to give a quantitative estimate of the health risk. Both FAO and WHO invite members who are responsible for assessing exposure. Both organizations establish listings of experts, called *rosters*; appointments are for a period of five years. Experts are selected from those rosters for each meeting, in which capacity they either attend the meeting as members or assist the Secretariat with preparatory work before the meeting and usually participate in the meeting itself. The selection of members for each meeting is made after a careful consideration of the scientific credentials of the various candidates, and a balance of scientific expertise and other experience that is considered essential considering the items on the agenda of the meeting. FAO and WHO meet the costs of experts' attendance at JECFA meetings.

Being a joint committee of FAO and WHO, the organizational framework of JECFA complies with the rules of both organizations. The selection process for experts is undertaken in mutual consultation by the Joint Secretariats. When calling for and selecting experts, FAO and WHO assure that selections complement each other. The selection process respects as well FAO and WHO policies on regional representation and gender balance.

Terms of Reference of the Committee

For food additives, including enzymes and flavouring agents, contaminants and naturally occurring toxicants, the Committee

(i) elaborates principles for evaluating their safety and for quantifying their risks;

(ii) conducts toxicological evaluations and establishes acceptable daily intakes (ADIs) or tolerable intakes for chronic exposure and other guidance values for acute exposure;

(iii) assess the performance, quality and applicability of analytical methods;

(iv) prepares specifications of purity for food additives; and

(v) assesses exposure of populations to chemical substances in food.

For residues of veterinary drugs in food, the Committee

(i) elaborates principles for evaluating their safety and for quantifying their risks;

(ii) establishes ADIs and other guidance values for acute exposure

(iii) recommends maximum residue limits (MRLs) for target tissues; and

(iv) determines appropriate criteria for and evaluates methods of analysis for detecting and/or quantifying residues in food.

Risk assessment

For food additives and veterinary drug residues, JECFA normally establishes ADIs on the basis of available toxicological data and other information. Specifications for the identity and purity of food additives are also developed, which help to ensure that the commercial product is of appropriate quality, can be manufactured consistently, and is equivalent to the material that was subjected to the toxicological testing.

For contaminants and naturally occurring toxicants, levels corresponding to 'tolerable' intakes such as the provisional maximum tolerable daily intake (PMTDI) or the provisional tolerable weekly intake (PTWI) are normally established when there is an identifiable no-observed-effect level. When a no-observed-effect level cannot be identified, the Committee aims to provide other advice depending on the circumstances and the data available.

For veterinary drug residues, maximum residue limits (MRLs) in target animal tissues, milk and eggs are developed taking into account Good Practice in the use of Veterinary Drugs. The application of these MRLs provides assurance that when the drug has been used properly, the intake of residues from animal produce is unlikely to exceed the ADI.

JECFA experts are expected to conduct extensive literature searches on the substances for consideration by the committee, in addition to the review of information submitted by sponsors and national governments.

JECFA also develops general principles and methods for the risk assessment of chemicals in food. To keep abreast in the variety of scientific disciplines necessary for the conduct of up-to-date risk assessments, continuous review and update of the evaluation processes are necessary. Moreover, JECFA plays an important role in the international harmonization of risk assessments of chemicals in food.

Reports and publications

An electronic summary with the main findings and conclusions of the meeting is published by the Joint Secretariat shortly after each meeting. Usually, the information is mainly in tabular format, including the details of ADIs and MRLs recommended. This is available on the website of JECFA at FAO and WHO.

The concise description of the key data used in the assessments, the evaluation of these data and the conclusions of the committee are published by WHO in the Technical Report Series. These reflect the view of the committee as a whole, albeit in rare events where one or more members cannot agree to the conclusions, the positions of the dissenting expert(s) and the reason for the disagreement will be recorded in the report.

Toxicological and exposure assessment monographs are published in the WHO Food Additive Series (FAS). These monographs contain the detailed description and evaluation of all the biological and toxicological data considered in the evaluation and provide references to the cited literature. A detailed exposure assessment is also included in the monographs.

The reports and toxicological monographs are available from the WHO JECFA website http://www.who.int/ipcs/publications/jecfa/en/.

Specifications monographs on the identity and purity of food additives developed at meetings and agreed on have been published in the Compendium of Food Additive Specifications (Food and Nutrition Paper 52) and are available from the FAO JECFA website http://www.fao.org/ag/agn/jecfa/database/cover.htm. A new Combined Compendium replaces the earlier edition and incorporates all the additions and revisions made since 1992, up to and including those contained in FNP 52 Addendum 13. It is being published as the first document under a new publication series, the FAO JECFA Monographs as Volume 1 - 3. Volume 4 of this first Monograph series will provide a reference for analytical methods and test procedures used in and referenced by the specifications and which replaces the previous Food and Nutrition Paper 5.

Monographs on veterinary drug residues, which summarize the data and the evaluations used for the recommendation of MRLs, have been published in the Food and Nutrition Paper Series 41 and are available from the FAO JECFA website http://www.fao.org/ag/agn/jecfa/jecfa_vetdrug_en.jsp. New monographs will be published in the FAO JECFA Monograph series from 2006 onwards.

Information on the activities and output from JECFA meetings are available at the dedicated JECFA websites at FAO http://www.fao.org/ag/agn/jecfa/index_en.stm and WHO http://www.who.int/ipcs/food/jecfa/en/ .

ANNEX E-3

REPLIES OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

21. What is the mandate of the International Agency for Research on Cancer?

According to the statute of the International Agency for Research on Cancer, "The objective of the International Agency for Research on Cancer shall be to promote international collaboration in cancer research. The Agency shall serve as a means through which Participating States and the World Health Organization, in liaison with the International Union against Cancer and other interested international organizations, may cooperate in the stimulation and support of all phases of research related to the problem of cancer." One of the Agency's functions is "the collection and dissemination of information on epidemiology of cancer, on cancer research and on the causation and prevention of cancer throughout the world."

22. Who are the members of the IARC?

According to the statute of the International Agency for Research on Cancer, "The Agency shall comprise: (a) the Governing Council; (b) the Scientific Council; (c) the Secretariat." The Governing Council shall be composed of one representative of each Participating State and the Director-General of the World Health Organization. In June 2006, the Participating States of the Agency are Australia, Belgium, Canada, Denmark, Finland, France, Germany, India, Italy, Japan, Norway, the Netherlands, the Republic of Korea, Spain, Sweden, Switzerland, the United Kingdom, and the United States. The Scientific Council is composed of a maximum of twenty highly qualified scientists, selected on the basis of their technical competence in cancer research and allied fields. The Secretariat consists of the Director of the Agency and such technical and administrative staff as may be required.

23. What are IARC Monographs? How are they prepared?

The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of human cancer.

IARC convenes an international, interdisciplinary Working Group of expert scientists to develop each volume of *IARC Monographs*. The Working Group writes a critical review of the pertinent scientific literature and an evaluation of each agent's potential to cause cancer in humans.

IARC Monographs are developed during an 8-day meeting whose objectives are peer review and consensus. Before the meeting, the Working Group searches the scientific literature and writes preliminary working papers for the critical review. At the meeting, four subgroups (exposure, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review these working papers and develop consensus subgroup drafts. Then the Working Group meets in plenary session to review the subgroup drafts and develop a consensus evaluation. After the meeting, IARC scientists review the final draft for accuracy and clarity before publication.

The evaluation is developed in steps. The subgroup of epidemiologists proposes an evaluation of the evidence of cancer in humans as *sufficient evidence*, *limited evidence*, *inadequate evidence*, or *evidence suggesting lack of carcinogenicity*. A subgroup of toxicologists and pathologists proposes an evaluation of the evidence of cancer in experimental animals, choosing one of the same descriptors. Combination of these two partial evaluations yields a preliminary default evaluation that the agent is either:

– *Carcinogenic to humans (Group 1)*
– *Probably carcinogenic to humans (Group 2A)*
– *Possibly carcinogenic to humans (Group 2B)*
– *Not classifiable as to its carcinogenicity to humans (Group 3)*
– *Probably not carcinogenic to humans (Group 4)*

When the epidemiological evidence is *sufficient*, the final evaluation is *carcinogenic to humans*, regardless of the experimental evidence. In other cases, the mechanistic and other relevant data are considered to determine whether the default evaluation should be modified, upwards or downwards. A subgroup of experts in cancer mechanisms assesses the strength of the mechanistic data and whether the mechanisms of tumour formation in experimental animals can operate in humans. The overall evaluation is a matter of scientific judgement, reflecting the combined weight of the evidence.

Working Groups are selected on the basis of (1) knowledge and experience and (2) absence of real or apparent conflicts of interests. Consideration is given also to demographic diversity and balance of scientific findings and views. Each potential participant completes the World Health Organization's Declaration of Interests, which IARC assesses to determine whether there is a conflict that warrants some limitation on participation. An expert with a real or apparent conflict of interests may not draft text that describes or interprets cancer data, participate in the evaluations, or serve as chair. IARC strives to ensure that the Working Group is free from all attempts at interference, before and during the meeting. This includes lobbying, written materials, and meals or other favours offered by interested parties. Working Group Members are asked not to discuss the subject matter with anyone outside the meeting and to report all attempts at interference.

24. Please briefly explain the groupings that are used to categorize "potentially carcinogenic agents"? What are the implications when an "agent" is placed in one of the IARC categories?

IARC uses the following groupings to characterize potentially carcinogenic agents:

Carcinogenic to humans (Group 1). This category is used when there is *sufficient evidence of carcinogenicity* in humans.

Probably carcinogenic to humans (Group 2A). This category is generally used when there is *limited evidence* in humans and *sufficient evidence* in experimental animals.

Possibly carcinogenic to humans (Group 2B). This category is generally used when there is *limited evidence* in humans or *sufficient evidence* in experimental animals, but not both.

Not classifiable as to its carcinogenicity to humans (Group 3). This category is generally used when there is *inadequate evidence* in humans and *inadequate* or *limited evidence* in experimental animals. Agents that do not fall into any other group are also placed in this category.

Probably not carcinogenic to humans (Group 4). This category is generally used when there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals.

Mechanistic and other relevant data also contribute to the grouping. Further details can be found in the Preamble to the *IARC Monographs* (http://monographs.iarc.fr).

25. Which of the six hormones at issue in this dispute (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate) have been evaluated by the IARC? Have any specific risks from the consumption of meat from cattle treated with these growth promotion hormones been assessed by the IARC?

IARC has evaluated steroidal estrogens as *carcinogenic to humans* (Group 1); for oestradiol-17β there is *sufficient evidence of carcinogenicity* in experimental animals (Volume 21, 1979; Supplement 7, 1987; Volume 72, 1999).

IARC has evaluated progestins as *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence of carcinogenicity* in experimental animals (Volume 21, 1979; Supplement 7, 1987).

For testosterone, IARC has determined that there is *sufficient evidence of carcinogenicity* in experimental animals and advised, "In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard testosterone as if it presented a carcinogenic risk to humans" (Volume 21, 1979).

Trenbolone acetate, zeranol, and melengestrol acetate have not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with these growth promotion hormones.

26. How does the work of the IARC feed into the work of national regulatory agencies or international bodies, in particular with respect to assessments of risks from the consumption of meat from cattle treated with the six growth promoting hormones at issue in this dispute?

The *IARC Monographs* are used by national and international health agencies as a source of information on potential carcinogens and as scientific support for their actions to prevent exposure to potential carcinogens. The *Monographs* are used by such national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes, and decide among alternative options for public health decisions.

WORLD TRADE ORGANIZATION

WT/DS321/R/Add.6
31 March 2008

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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex F to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex B: Add.2
- Annex C: Add.3
- Annex D: Add.4
- Annex E: Add.5
- Annex G: Add.7

ANNEX F

COMMENTS BY THE PARTIES ON THE REPLIES OF THE SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC TO QUESTIONS POSED BY THE PANEL AND COMMENTS BY THE PARTIES ON THE OTHER PARTIES' COMMENTS

ANNEX F-1

COMMENTS BY THE EUROPEAN COMMUNITIES ON THE REPLIES OF THE SCIENTIFIC EXPERTS TO QUESTIONS POSED BY THE PANEL

(30 June 2006)

A. GENERAL DEFINITIONS

Q1. Please provide brief and basic definitions for the six hormones at issue (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate), indicating the source of the definition where applicable.

EC Comments

Dr. Boisseau's reply does not consider any progress in toxicological knowledge concerning these hormones, and in particular estradiol, since the 70th and 80th JECFA reports. Since then new data concerning residues in tissue and their toxicological impact have been published. In his answer, he has only adopted a narrow regulatory definition. More specifically, as regards oestradiol, aromatization of androgens in estrogens is also very significant in adipose tissue. In his definitions, the sites of production in the human body is limited to the primary source and does not dwell on variability over the life span of an individual. Furthermore, his definition does not stress that Zeranol is a very potent estrogen. Zeranol is not a "natural estrogen" that humans are exposed to. In fact, great care should be taken to avoid the presence of fusarium molds in animal feed and especially in products for human consumption. As regards the implantation of these hormones, he uses simple present tense ("the ear is discarded") when precisely this is not known nor it is sure that it happens in practice in all cases. He should therefore have said that "the ear should be discarded at slaughter". Moreover, implantation can be made at the dewlap level, not only at the ear one, especially in case of multiple implantations. Furthermore, in some new recommendations of trenbolone use, it is possible to proceed to repeated implantation of steers or heifers.

Q2. Please provide definitions for the following terms as they relate to the hormones at issue, indicating the source of the definition where applicable: anabolic agents, steroids, steroidal oestrogens, parent compounds/metabolites, catechol metabolites, mitogenicity, mutagenicity, androgenic/oestrogenic activity, genotoxicity, genotoxic potential, carcinogenicity, and tumorigenicity. In your replies, please be sure to identify and describe any relevant differences between the terms.

EC Comments

Dr. Boisseau's reply that "In my e-mail of 26/04/06, I have indicated that I did not think that I am in the position to reply to this question" calls into question the reliability of his answer to question no 1 and indeed to the other questions. As the EC has pointed out during the selection procedure, Dr. Boisseau does not posses any expertise on these substances, as he does not appear to have carried out any specific research on these substances during his professional life. Dr. Boisseau has explicitly admitted it in his e-mail to the Panel secretariat where he wrote: "*I did not join any publications as I have none on hormones*".

B. RISK ASSESSMENT TECHNIQUES

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

EC Comments

The European Communities agrees with the statement by Dr. Boisseau that currently there is no international guidance document relevant to the conduct of a risk assessment with respect to veterinary drug residues and in particular the six hormones under consideration. Indeed, the documents to which Dr. Boobis refers to in his reply are not "assessment techniques developed by the relevant international organizations", in the sense of Article 5.1 of the *SPS Agreement*. They are informal ad hoc papers without any legal value. Moreover, when the European Communities evaluated these hormones, it applied its standard legislation for the evaluation of this type of substances, which complies fully with the general definitions of risk analysis as described in the Codex Alimentarius' latest Manual of Procedures.

Moreover, Dr. Boisseau's statement that "*the situation is similar in the European Union*" and that "*The CVMP has assessed all the pharmacologically active substances used in veterinary medecine without any written guideline about risk assessment*" is wrong. It is not the CVMP (Committee on veterinary medicinal products) which is responsible for these hormones when administered for animal growth promotion, but it has been the SCVPH (scientific committee on veterinary measures relating to public health). This latter Committee, and the European Communities in general, have been applying advanced principles and techniques of risk analysis which Codex Alimentarius is only now considering of formally putting in practice. See for instance the European Commission Decision 97/579/EC of 23 July 1997 which set up scientific committees in the field of consumer health and food safety which has established the SCVPH (OJ L 237, 28.8.1997, p. 18-23) and the Opinion of the Scientific Steering Committee on harmonisation of risk assessment procedures adopted on 26-27 October 2000, which can be found at http://ec.europa.eu/food/fs/sc/ssc/out82_en.html. These advanced principles of risk analysis have been routinely applied by the European Communities for quite some time well before 1997.[1] They were applied when the SCVPH evaluated these six hormones in 1999, 2000 and 2002, and have since then formally been restated in the relevant EC legislation, in particular Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 31, 1.2.02, p. 1-24, in particular Article 6.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)].

EC Comments

As already explained above in its comments to the replies to question No 3, the European Communities agrees with Dr. Boisseau's reply that "there is no Codex standard specifically on the risk assessment of effect of residues of veterinary drugs". Neither the work of IPCS nor the

[1] See, e.g., Commission Directive 93/67/EEC of 20 July 1993 laying down the principles for assessment of risks to man and the environment of substances notified in accordance with Council Directive 67/548/EEC, OJ L 227, 8.9.1993, p. 9-18.

Environmental health Criteria no 70 nor the monograph published in the WHO series no 43, mentioned by Dr. Boobis and Dr. Guttenplan, respectively, constitute legally binding "assessment techniques" for risk assessment in the sense of Article 5.1 of the *SPS Agreement*. The EC has been much more advanced than JECFA in the application of generally acceptable techniques for risk analysis, as explained in the references to the relevant EC legislation in the previous question No 3. The EC documents mentioned above, although publicly accessible, can be made available to the Panel and its experts upon request.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) and explain how they differ.

EC Comments

The European Communities submits that the Panel's question is of little relevance to the issues under consideration in the present proceedings. Indeed, the Panel's question appears to ignore the fact that the Appellate Body in the *Hormones* case has clarified that the term "risk assessment" in the *SPS Agreement* is wider in scope because it covers also evidence, considerations, objectives and factors that are also taken into account at the "risk management" phase.[2] Consequently, the answers of all scientists do not take into account the legal requirements of the *SPS Agreement* in this area, as interpreted by the Appellate Body. However, the European Comunities has in any case followed the three components of risk analysis, as explained above and in its reply of 3 October 2005 to question No 24 of the Panel.

Moreover, none of the replies by the scientists describes what is actually going on in Codex. The reality is that JECFA performs, most of the time, as it did with regard to these hormones, both risk assessment and risk management functions (something which Dr. Boisseau admits), thus the subsequent decisions/recommendations by the Codex Alimentarius Commission become a mere formality. Indeed, JECFA's reports and monographs are drafted in such a way as to leave practically no room to the members of the Codex Alimentarius Commission to decide on the appropriate level of health protection and the risk management options that are available to its members. That is another reason for which the European Communities decided that the Codex recommendations on these hormones could not achieve the level of health protection considered appropriate in its territory.

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

EC Comments

The European Communities does not understand the relevance of this question for the purposes of these disputes and the corresponding replies of Dr. Boisseau and Dr. Boobis. This type of formal distinction between the various components of risk assessment are not mentioned in the *SPS Agreement* and they are clearly not legally binding, since they are not risk "assessment techniques" in the sense of Article 5.1 of the *SPS Agreement*. Moreover, as the Appellate Body has held in the *Hormones* case (at para. 181), to the extent these distinctions are used "to achieve or support what appears to be a restrictive notion of risk assessment" this has no textual basis in the SPS Agreement. More importantly, however, if these four steps are not formally identified in the risk assessment document of a member, this does not mean that the risk assessment of that member is faulty or scientifically unsound. For instance, the statements by the above 2 scientists appear to discard the relevance of some residues that are not pharmacologically active but may interfere with normal metabolic functioning of cells given their intrinsic chemical potential to form covalent adducts to

[2] *See* Appellate Body Report in EC - *Hormones*, at paras. 181 and 206.

biomolecules (trenbolone for example which gives a high level of protein adducts). Normally, this biological impact should be considered separately and in addition to the hormonal effects. But until now, this has never been done by JECFA and the defending parties when they evaluated these hormones for animal growth promotion purposes. Hence, it is difficult in this context to know what is really a marker residue of a compound having some toxic impact that are not at all related to hormonal effects.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations, in your view, addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? Have they been addressed in the 1988 and 1999 JECFA risk assessments of these hormones? [see Canada's comments in para. 72 of its Rebuttal Submission]

EC Comments

The European Communities notes first that Dr. Boisseau admits that "in 1987 and 1999, at the time of the assessment of oestradiol-17β, there was no risk assessment guidance available on this issue". Even so, he goes on to argue that neither in 1987 nor in 1999 JECFA considered this kind of non-linear situation, despite the fact that it had found in its 1999 report that "oestradiol-17β has a genotoxic potential." However, this approach of JECFA is scientifically unsound, as Dr. Boobis now accepts when he says that today "in practice, it is likely that as veterinary drug residues in food are avoidable by not using the drug, the Committee would have declined to establish an ADI".

The European Communities notes, however, that there are basic flaws in the replies of both Dr. Boisseau and Dr. Boobis. Indeed, the accumulation of so much new peer-reviewed evidence since 1999 establishes clearly that oestradiol-17β is a direct carcinogen and does not act only through hormonal receptors. In addition to the peer-reviewed studies mentioned in the 1999, 2000 and 2002 EC risk assessments, it would be appropriate to refer also to the work of Hari K. Bhat, Gloria Calaf, Tom K. Hei, Theresa Loya, and Jaydutt V. Vadgama: *Critical role of oxidative stress in estrogen-induced carcinogenesis*, published in the Proceedings of the National Academy of Sciences, Vol. 100 (2003) 3913-3918, demonstrating the necessary role of catechols of estradiol or other catechols (2/4-hydroxy-estradiol-alpha produced from estradiol-alpha, menadione) in induction of oxidative stress to induce tumors in the hamster kidney carcinogenesis model. See also the two papers by J. Russo and his co-workers: *17β-Estradiol is carcinogenic in human breast epithelial cells*, and *Estrogen and its metabolites are carcinogenic agents in human breast epithelial cells*, published in the Journal of Steroid Biochemistry & Molecular Biology, vol. 80 (2002) 149-162 and vol. 87 (2003) 1-25, respectively.

From a more systematic point of view, the views of Dr. Boobis can also be criticized because a threshold is a theoretical concept that provides the justification for the use of the NOAEL and thus the ADI. In the work of JECFA, the NOAEL is perceived as evidence of the practical revelation of a threshold. But a true threshold can only be established with an infinitely large group of animals: thus, the dose distance between the true threshold and the NOAEL cannot be established. In a genetically and phenotypically heterogenous human population, there is a risk from endogenous hormone – induced adverse outcomes. Additionally, there must be a distribution of both consumption of meat and hormone response sensitivity in the human population. We know that endogenous hormones in animals and humans are known to cause a wide variety of adverse effects from reproductive function to malignancies. These considerations demonstrate that some fraction of the population will be at higher risk for hormone-related adverse outcomes, no matter the dose, due to consumption of

hormone-implanted meat. A number of publications, some of which have been submitted by the European Communities to this Panel, have explored the threshold concept and the activity of hormones at very low doses. These are:

Gaylor, D. W., Sheehan, D. M., Young, J. F. and Mattison, D. R.: The threshold dose question in teratogenesis (Letter). Teratology, 38:389-391, 1988.

Sheehan, D. M., and vom Saal, F. S.: Low dose effects of endocrine disruptors- a challenge for risk assessment. Risk Policy Report, 31-39, issue of Sept.19, 1997.

Sheehan, D. M., Willingham, E., Gaylor, D., Bergeron, J. M., and Crews, D.: No threshold dose for oestradiol-induced sex reversal of turtle embryos: How little is too much? Environmental Health Perspectives 107:155-159, 1999.

Sheehan, D. M.: Activity of environmentally low doses of endocrine disruptors and the Bisphenol A controversy: Initial results confirmed, in Proc. Soc. Exp. Biol. Med. 224:57-60, 2000.

Blair, RM, Fang, H, Gaylor, D, Sheehan, D. M.: Threshold analysis of selected dose-response data for endrocrine disruptors, in APMIS 109:198-208, 2001.

Q8. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please identify and describe any steps that are taken in the risk assessment process to build a margin of safety into the final recommendation.

EC Comments

The replies of Dr. Boisseau and Dr. Boobis are theoretical statements with little scientific relevance as regards the safety of these hormones. For instance, the appropriate studies in humans would require a huge study population, and would be seriously confounded by medical treatments with hormones and environmental exposures to hormones. Also the conclusion that there is a threshold for hormone action in the absence of other sources of hormone cannot provide a sound scientific basis in order to conclude that endogenous hormones are below the threshold for all actions of the hormones. Therefore, added hormone from implanted beef should increase risk for endpoints that are already occurring from endogenous hormones. Appreciable risk is a subjective decision, as are the 10-fold safety margins. Because of the small numbers of animals on studies, the resolution is generally low.

More specifically, the evidence used by JECFA in the evaluation of these hormones is too old (dating from the 1970s) and has been obtained with outdated detection methods to be relevant today. Dr. Boisseau also writes that "*...taking into consideration the diversity of humans, resulting from the sex, age, race, which can lead to different sensitivity...*", but JECFA did not take the low endogenous levels and thus the high sensitivity of children into account. Also Dr. Boobis states that "*where there was an identifiable sub-group who might reasonably be expected to be more sensitive than the group in whom data were obtained, for example children relative to adults, an extra factor was applied*." Indeed, the JECFA expert committee that examined these hormones did not include any physicians and child endocrinologists! It can be argued that for most chemical compounds, such as pesticides, the knowledge on their potential toxicity resides with toxicologists. However, when we are dealing with the natural hormones and compounds that directly affect the endocrine system, the knowledge on how they potentially can affect humans is a part of the daily work of paediatricians and other physicians. Thus, it is essential that persons with a medical background are present in the JECFA committee (see more on this below). Dr. Boisseau also writes something about low oral activity of 17β-oestradiol, but that is simply not scientifically correct as demonstrated below (comment in relation to question 43). For instance, oral contraceptives and some hormone replacement therapy are taken by the oral

route and are shown to be very active. This demonstrates that oestradiol and progesterone are bioavailable through the oral route.

Q9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

EC Comments

The Canadian statement cannot be scientifically correct in the unqualified manner in which it is expressed and certainly is not correct as regards the six hormones under consideration. It would all depend on when JECFA's scientific data base is considered to be complete and that there are no outstanding scientific issue. For example, when JECFA evaluated in 1988 these hormones, it considered unnecessary to establish an ADI, presumably because it considered that there was no outstanding scientific issue. However, in its 1999 evaluation of the three natural hormones JECFA changed its evaluation and this time established an ADI. Both in 1988 and in 1999 JECFA's evaluation was based on the assumption that these substances act only through the hormonal receptors. However, this assumption is certainly incomplete and scientifically incorrect because it is today generally accepted that some of these hormones are genotoxic and can cause cancer directly. Furthermore, as already explained above, the ADI and MRLs that JECFA established in 1988 and in 1999 for the three synthetic hormones do not take into account the low endogenous levels and thus high sensitivity of prepubertal children. In conclusion, there are so many examples of cases where JECFA has set an ADI because it considered its scientific data base to be complete and that there were no outstanding scientific issues, but it had subsequently to change its mind in the light of more accurate reading of the evidence or more recent scientific data. A good recent example is the case of Carbadox, cited by the European Communities in paras. 150 and 151 of its 2nd Written Submission in the US Panel. It follows that the issue of when the scientific data base is complete can be very subjective and prone to many errors of which JECFA's assessments are certainly not immune.

Q10. In para. 129 and 168 of its Replies to the Panel Questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not". Does Codex have risk management options other than (1) the establishment of an MRL, (2) establishing that an MRL is not necessary or (3) no recommendation?

EC Comments

The European Communities considers that the reply of Dr. Boisseau confirms that JECFA has a narrow mandate, even if it frequently oversteps its role and proposes also risk management measures, thus leaving practically no option to Codex Alimentarius Commission and its members than to follow its narrow recommendations to adopt or not an MRL. What is also important to note is that JECFA has not considered as part of its narrow mandate to examine whether there is any likelihood of misuse or abuse of these hormones and whether the identified risks to human and animal health from the use of these hormones for growth promotion by far exceed any potential benefits.

Q11. What should, in your view, be the components of a qualitative risk assessment, compared with a quantitative risk assessment? [see para. 82 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with the statement by Dr. Cogliano. The statements by Dr. Boisseau and Dr. Boobis are simply contrary to the findings of the Appellate Body in the 1998

Hormones case, where it held that a qualitative risk assessment is equally acceptable under the SPS Agreement and that it does not require the same type of analysis as a quantitative risk assessment. More generally, the issue of whether a threshold model or a non-threshold model is used is critical in determining risk. The literature on no-threshold cited above, in addition to the no-threshold models used for example for PCBs and dioxin, are more appropriate than the current procedures applied by JECFA. For instance, endogenous estrogens are active at inducing some responses in most, if not all, age and population groups. Additivity of exposure to endogenous and exogenous hormones will necessarily result in increased risk at any exogenous dose, no matter how low. Interestingly, the US EPA uses no-threshold models for non-genotoxic chemicals, such as dioxins and PCBs, due to a combination of very long half-lives and activity at very low doses. The European Communities submits that consumption of hormone-treated beef at regular intervals will provide continual or intermittent exposure of estradiol and other growth hormones and thus increase risk and undermine its high level of health protection from these substances.

Q12. How is scientific uncertainty addressed in risk assessments in general? With respect to the assessment of risks from the consumption of meat treated with the growth promotion hormones at issue, how has scientific uncertainty been considered by JECFA/Codex ? How does it differ from the way it has been considered by the European Communities in its assessment of risks from the consumption of meat treated with the growth promotion hormones at issue?

EC Comments

The European Communities disagrees with the statements by Dr. Boisseau and Dr. Boobis because of their extremely narrow understanding of the concept of scientific uncertainty. They both consider that scientific uncertainty is adequately addressed by JECFA when applying the so-called safety factors. There is however now almost universal agreement that this approach is not scientifically correct. A state of uncertainty may result from a number of factors, such as lack, incomplete or contradictory data. It is not the quantity but the quality of the data that is important. It is possible that an issue that was thought to be scientifically clear to become uncertain as more data become available. When scientific uncertainty is understood in this sense, this cannot be tackled with the application of so-called safety factors or margins, especially for countries that wish to apply a high level of health protection. For example, the genotoxic and carcinogenic potential of oestradiol-17β cannot be adequately addressed by the safety factors applied by JECFA, because the underlying scientific uncertainty about the mechanisms causing cancer are not amenable to quantification so as to be adequately addressed by the safety factors (there is always the risk of under-inclusion). Another example is that when JECFA evaluated the three natural hormones in 1988 and in 1999 and decide not to set a ADI and a MRL, it based its evaluation concerning endogenous production of these hormones by prepubertal children on very old data from 1974 (citing the paper by Angsusingha K. et al: *Unconjugated estrone, estradiol, and FSH and LH in prepubertal and pubertal males and females*, Journal of Clinical Endocrinology and Metabolism, 39: 63-68 (1974), as reported in the 32nd report of JECFA published in the WHO technical report series no 763, page 32). However, the data reported by Angsusingha et al. are no longer valid in view of the more recent findings with more accurate detection and measurement tools available (see the discussion in paras. 121-122 of the EC 2nd written submission in the US panel and the references thereto to the papers by Klein and Klein and by Anderson and Skakkebaek of 1994, 1999 and 2005, respectively).

It follows from the above that the statement by Dr. Boisseau that "for the three natural hormones, oestradiol-17β, progesterone and testosterone, JECFA has decided that the margin of safety deriving from the values of the established ADIs and from a maximum estimated intake of residue was such that it was not necessary to set up MRLs" is plainly wrong. His statement that the European Communities "did not consider any scientific uncertainty" is also false, because a careful reading of

the 1999 risk assessment by the SCVPH shows that the reasons for which that scientific committee considered that oestradiol-17β is a proven carcinogen and that the uncertainty regarding the other five hormones (resulting from the lack of data or the presence of contradictory data) are properly explained and taken into account.

Dr. Boobis also made the equally false statement that: "… the EC assessment of the hormones did not go as far as including some of the considerations for uncertainty used by JECFA because of the conclusion that there was insufficient information to determine whether there was a threshold for the carcinogenic effects. However, for some of the compounds this was based on the results of a small number of non-standard tests of genotoxicity, with equivocal of very weak responses. It is not clear whether the EC applied a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking account the totality of the available data, as was the case by JECFA." Indeed, the three risk assessments of 1999, 2000 and 2002 by the SCVPH did consider the totality of the available data. In fact, Dr. Boobis' reply does not discusses at all that since 2002, the US authorities concluded that "steroidal estrogens are known to be human carcinogens based on sufficient evidence of carcinogenicity in humans, which indicates a causal relationship between exposure to steroidal estrogens and human cancer." For this reason, the US 2002 Report on Carcinogens (RoC) lists steroidal estrogens as known to be human carcinogens with the clarification that this listing now "supersedes the previous listing of specific estrogens in and applies to all chemicals of this steroid class." Moreover, in the same 2002 US Report it is stated that: "Veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food producing animals to above their normal levels."[3] So, the 2002 US Report on Carcinogenesis contradicts the allegations made by the US and Canada in these proceedings, which appear to be supported by Dr. Boobis, that the additional burden of residues coming from eating hormone-treated meat is so small that it would make no difference, compared to the level of endogenous production.

Furthermore, neither Dr. Boobis nor Dr. Boisseau mention the fact that the IARC has classified oestradiol-17β in Group 1 as carcinogenic to humans because there is sufficient evidence of carcinogenicity and progesterone and testosterone in Group 2B as possibly carcinogenic to humans. It is therefore a surprising statement by Dr. Boobis that the EC "*did not apply a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking into account the totality of the available data, as was the case by JECFA*", because it is precisely JECFA's evaluation that is based on old and outdated data and does not examine the totality of the available evidence. Moreover, the argument of Dr. Boobis that a WTO member has to apply a "weight of evidence approach" is legally incorrect. It is not very clear what Dr. Boobis means by this approach, but it must not be taken to mean that only the mainstream scientific views should be accepted or that such an approach could remedy the identified scientific uncertainty. Moreover, this approach would amount to forcing WTO members to dismiss or ignore minority scientific views, which has clearly been rejected by the Appellate Body in the 1998 *Hormones* case, where it held that:

> "Article 5.1 of the SPS Agreement does not require that the risk assessment must necessarily embody only the view of a majority of the relevant scientific community. In some cases, the very existence of divergent views presented by qualified scientists who have investigated the particular issue at hand may indicate a state of scientific uncertainty. In most cases, responsible and representative governments tend to base their legislative and administrative measures on "mainstream" scientific opinion. In other cases, equally responsible and representative governments may act in good faith on the basis of what, at a given time, may be a divergent opinion coming from qualified and respected sources. By itself, this does not necessarily signal the absence of a reasonable relationship between the SPS measure and the risk assessment,

[3] Available at http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540.

> especially where the risk involved is life-threatening in character and is perceived to constitute a clear and imminent threat to public health and safety." (at para. 194 of the AB report)

On a more specific point, Dr. Boisseau is apparently committing the same error as the defending parties because he keeps referring to the "differences in the interpretation of data, as illustrated by the differing conclusions of the CVMP (1999) and the SCVPH (1999)", without knowing that the CVMP has evaluated some of the natural hormones in different preparations and for different purposes (therapeutic or zootechnical use) and its findings are not relevant for the use of the six hormones when administered for animal growth promotion (for which the competence to assess resided with the SCVPH).

C. ASSESSMENT OF OESTRADIOL-17B

Q13. To what extent, in your view, does the EC risk assessment identify the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol-17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice? To what extent does the EC risk assessment evaluate the potential occurrence of these adverse effects?

EC Comments

The European Communities is surprised by the affirmative tone in the statements by Dr. Boisseau and Dr. Boobis that the genotoxic effect of oestradiol-17β is associated with its hormonal activity, when JECFA itself was more cautious when stating that "the carcinogenicity of oestradiol-17β is *most probably* a result of its interaction with hormonal receptors" (emphasis added). Their statements become even more questionable in that they both do not take into account nor do they discuss the most recent and growing scientific evidence linking, directly or indirectly, oestradiol-17β and the other hormones with increased risk of cancer. Unlike what Dr. Boisseau states, there is growing evidence from in vivo studies, (e.g. by Bhat et al., already mentioned above, published in PNAS 100 (2003) 3913-3918) which has shown that estradiol is responsible for both initiation and promotion of tumors *in vivo*. Moreover, carcinogenicity of estrogens is primarily due to oxidative stress/DNA adduct formation caused by the catechols metabolites of estrogens. The role of receptor stimulation is only invoked in the promotion stage of carcinogenesis. For this reason, it is also necessary to consider estradiol-alpha as residues susceptible to be metabolised in consumer in catechol derivative with the same potency as estradiol to give adducts or to induce oxidative stress.

As already explained, it needs to be recalled again that estradiol has been classified as a Group 1 carcinogen by IARC and the results from numerous epidemiological studies support the association of elevated prolonged exposure to endogenous and exogenous estrogen with breast cancer. These studies are supported by studies in experimental animal models that not only include the Syrian hamster kidney model and mouse uterus model, referred to by Dr. Guttenplan in his response to Q. 14, but also the ACI rat (J. Endocrinology, 183, 91-99, 2004) and the ERKO/Wnt mouse (J. Steroid Biochem. Mol. Bio., 86, 477-486, 2003). In both of the latter models a clear dependence of the tumors on estradiol was shown and, in the latter model, the results show that the mammary tumors arise through effects of estradiol not mediated through the estrogen receptor (ER) since the mice lack ER expression.

So there seems now to be agreement that exposure to oestradiol-17β may increase the sensitivity to other carcinogens and thus increase the cancer risk (simultaneous or later in life). One more example

is the ENU-mediated induction of endometrial adenocarcinomas (Takahashi et al., 1996),[4] where simultaneous exposure to oestradiol-17β significantly increased the yield of adenocarcinomas. More recently, the concept of tissue stem cells, as the cells where breast cancer originates, has led to a new concept linking breast cancer risk with the stem cell potential as a measurable variable of the 'fertile soil' for cellular transformation. It is suggested that low-dose estrogen exposure leads to increased proliferation of the tissue stem cells and, since it is hypothesised that the number of potentially carcinogenic tissue stem cells determines the risk of getting the cancer, thereby to an increased risk of breast cancer later in life. This aspect is not at all considered by these experts.[5]

Other adverse effects on human health have also been established. Thus, there are strong data linking administration of very low doses of oestradiol-17β to pre-pubertal girls to changes in growth pattern despite the fact that serum levels of oestradiol-17β remained below the detection limit (Lampit et al., 2002).[6] This may affect the risk for breast cancer later in life because it has been convincingly demonstrated that prepubertal growth rates significantly influence the breast cancer risk (Ahlgren et al., 2004).[7]

The European Communities also disputes the statements by Dr. Boobis that the EC's risk assessment used "speculative assumptions" about misuse or abuse of the product, that no adequate assessment of exposure following use according to GVP was undertaken, or that there was no attempt to estimate the potential occurrence of adverse effects in humans following exposure to levels of the hormones found in meat from treated animals. The experiments conducted by the EC and its findings are based on realistic conditions of use and demonstrate that GVP is frequently not respected in the defending members. The EC exhibits Nos 12, 16, 17, 52, 67, 68, 69 and 73 provide concrete evidence of abuse and misuse of these hormones by the both the US and Canada.

The European Communities agrees with the statement by Dr. Guttenplan that there are basically no direct epidemiological studies comparing matched populations consuming meat from untreated and hormone-treated cattle. However, apart from the ethical concerns, it is difficult to conduct such direct experiments in the presence of so many other confounding factors because of feasibility limitations for observational studies. This being said, it is common that in animal models used in carcinogenesis bioassays (rats and mice) one of the more sensitive tissues for tumorigenesis is liver. At the present time, however, the classification of chemicals as carcinogens does not require that the tumors produced in the bioassays are the same as would appear in humans; chemicals are classified as carcinogens when they cause a significant increase in tumors regardless of the tissue.

Q14. In your view, does the risk assessment undertaken by the European Communities on oestradiol-17β follow the Codex Guidelines on risk assessment, including the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization with respect to oestradiol-17β?

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[4] See Takahashi M, Iijima T, Suzuki K, Ando-Lu J, Yoshida M, Kitamura T, Nishiyama K, Miyajima K, Maekawa A.: Rapid and high yield induction of endometrial adenocarcinomas in CD-1 mice by a single intrauterine administration of N-ethyl-N-nitrosourea combined with chronic 17 beta-estradiol treatment, in Cancer Lett. 104:7-12 (1996).

[5] *See* Smalley M., Ashworth A.: *Stem cells and breast cancer: A field in transit*. Nat Rev. Cancer. 2003, 3(11) :832-44, and Baik I., Becker P.S., DeVito W.J., Lagiou P., Ballen K., Quesenberry P.J., Hsieh C-C.: *Stem cells and prenatal origin of breast cancer*. Cancer Causes and Control 15: 517–530 (2004).

[6] *See* Lampit M., Golander A., Guttmann H., Hochberg Z.: *Estrogen Mini-Dose Replacement during GnRH Agonist Therapy in Central Precocious Puberty: A Pilot Study*. The Journal of Clinical Endocrinology & Metabolism 87:687–690 (2002).

[7] *See* Ahlgren M., Melbye M., Wohlfahrt J., Sorensen T.I.: *Growth patterns and the risk of breast cancer in women*. N. Engl. J. Med. 351:1619-26 (2004).

EC Comments

The European Communities disagrees with the statement by Dr. Boobis because from a careful reading of the 1999, 2000 and 2002 risk assessment by the SCVPH it is obvious that it has followed the four steps of risk assessment when it carried out its qualitative risk assessment. That this is so is also confirmed by the statement by Dr. Boisseau although Dr. Guttenplan gives it a "mixed rating" in following the Codex guidelines which became available in 2003.

For the sake of completeness, however, it should also be clarified that Dr. Guttenplan has not considered the studies on the ACI rat and ERKO/Wnt mouse. The studies carried in experimental animal models do not only include the Syrian hamster kidney model and mouse uterus model, referred to by Dr. Guttenplan, but also the ACI rat (J. Endocrinology, 183, 91-99, 2004) and the ERKO/Wnt mouse (J. Steroid Biochem. Mol. Bio., 86, 477-486, 2003). In both of the latter models a clear dependence of the tumors on estradiol was shown and, in the latter model, the results show that the mammary tumors arise through effects of estradiol not mediated through the estrogen receptor (ER) since the mice lack ER expression. In addition, there are several additional models in transgenic mice where mammary tumor formation has been shown to be estrogen dependent.

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

Q15. Does the identification of oestradiol-17β as a human carcinogen indicate that there are potential adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes? Does your answer depend on whether good veterinary practices are followed? [see para. 206-207 of EC Rebuttal Submission (US case), para. 121 of EC Rebuttal Submission (Canada case), paras. 97-98 of EC Replies to Panel Questions, paras. 76-77, 150 and 155-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission]

EC Comments

The European Communities notes the different and in some parts contradictory statements by the four experts that replied to this question. It agrees with the reply of Dr. Cogliano. It also agrees that if GVP is not followed, the risk is even higher. For the benefit of Dr. Guttenplan, the EC would clarify that the term "potential" in the SPS Agreement has indeed been interpreted by the Appellate Body in the 1998 *Hormones* case to mean "possible" (at para. 185 of the report).

The position of Dr. Boobis and that of Dr. Boisseau is conditioned by their understanding that oestradiol-17β is causing cancer only through receptor mediated processes. This hypothesis is however scientifically no longer tenable in light of more recent evidence cited by the European Communities. Reading between the lines of their replies, however, these two experts also do not seem to deny completely the existence of possible adverse effects from residues in meat from animals treated with this hormone for growth promotion purposes.

Q16. Does the scientific evidence relied upon in the SCVPH Opinions support the conclusion that carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity? [see para. 148 of the EC Replies to Panel Questions and paras. 35-40 and 46 of US Rebuttal Submission]

EC Comments

The European Communities disagrees with the statements of Dr. Boisseau and Dr. Boobis. For Dr. Boisseau there is only one other authoritative source of comparison, that is the JECFA reports, irrespective of the outdated nature of its reports and old data on which they are based. In his long reply, Dr. Boisseau interprets lack of data as lack of adverse effects. Is this really a valid approach that is followed by JECFA? Dr. Boisseau further criticises the SCVPH assessments on the ground that they did not include a "quantitative assessment" of the risk or that it did not establish its genotoxicity with data from experiments *in vivo*. Dr. Boisseau does not probably know that the Appellate Body has held that a *qualitative* assessment of risk is acceptable for the purposes of the *SPS Agreement*. Moreover, he does not consider the other more recent evidence cited by the European Communities showing the direct genotoxic potential of oestradiol-17β, progesterone, zeranol and most possible testosterone. As regards MGA and trenbolone acetate the evidence may be inconclusive but there are sufficient indications to treat them as such, despite the serious gaps in our scientific knowledge.

Amongst the flaws in Dr. Boobis' reply is that he criticises the EC assessment for not having evaluated these hormones "on a weight of evidence" basis. However, this type of criticism is scientifically inaccurate and legally inappropriate for the purposes of the *SPS Agreement* for the reasons explained in the EC's comments on the reply to question no 12 above. Moreover, he states that "*JECFA concluded that whilst oestradiol is a human carcinogen, its mode of action is such that there would be no appreciable risk of cancer at exposures up to the ADI*". JECFA's statement that there is no appreciable risk is a subjective expression, but it does confirm that there is excess risk due to added hormone. Again, "appreciable risk" is a qualitative and not a quantitative term, and thus fails to provide the necessary assurance that the EC's level of protection of no risk from residues of these hormones in meat will be achieved.

Dr. Guttenplan makes a more informed assessment of the scientific situation and concludes that the more recent evidence cited by the European Communities does support the finding that the genotoxic action of these hormones is not related only to their hormonal activity. Indeed, Dr. Guttenplan acknowledges that the evidence is now sufficient to support a role for the estrogen metabolites which include the genotoxic, mutagenic estrogen quinones in estrogen carcinogenicity (New Eng. J. Med., 354, 270-282, 2006).

Q17. Could you comment on Canada's statement that "the studies commissioned by the European Communities also failed to find evidence of "catechol metabolites" – that is the oestradiol metabolites identified as the source of the genotoxic potential – in meat from treated animals"? What would be the implication of an absence or presence of catechol metabolites? [see para. 102 of Canada Rebuttal submission, EC Exhibit 51A]

EC Comments

The European Communities agrees with the statements by Dr. Guttenplan and Dr. Cogliano. Indeed, it is known that, in contrast to humans, cattle do not efficiently metabolize estradiol to catechols and this apparently explains the very low levels of catechols in meat. Furthermore, the real problem is not to prove the presence of catechols as residues in edible tissues, but to determine the real part of estradiol, estradiol-alpha or estrone that will be metabolised in catechols in target tissues. Due to their structure, catechols metabolites eventually found as residues in edible tissue of treated cattle would exist more probably as glutathione conjugates and only a small part of them as glucuronides. Nevertheless, due to their chemical reactivity, catechols as such are not stable enough because they are already transformed in a more stable form. Therefore, more worrying from the human health point of view is the part of estrogens (estradiol, estradiol-alpha or estrone) which will be metabolised in catechol derivatives in target tissues. This is the reason for which it is necessary to perform a complete residue analysis with

more powerful detection methods. Thus, as Dr. Guttenplan correctly states, the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity.

Indeed, it is important to keep in mind that in the ACI rat, mammary tumors were not induced by the administration of the catechol metabolites of estradiol, but only by administration of estradiol. Furthermore, the fact that exposure to the catechol metabolites does not cause mammary tumorigenesis does not necessarily negate the possibility that the catechol metabolites formed in mammary tissue play a role in mammary tumorigenesis. This is because administered metabolites may not reach levels in mammary tissue comparable to those achieved by metabolism of estradiol to the catechols within the mammary tissue itself. Analysis of both human and mouse mammary tissue has demonstrated the presence of catechol metabolites and conjugates of estrogen quinones with glutathione, the latter demonstrating that oxidative metabolism of estradiol to the catechols and their further oxidative metabolism to reactive estrogen quinones occurs in normal human and mouse mammary tissue (Carcinogenesis, 22, 1573-1576, 2001; Carcinogenesis, 24, 697-702, 2003).

As regards the statements by Dr. Boisseau and Dr. Boobis, they can only be explained by their lack of specific expertise on these hormones, as they have not carried any specific research on these substances in their professional life. Their statements therefore should carry no weight. Indeed, it should be recalled that during the 1997 panel report on hormones, one of the experts for the panel (Dr. G. Lucier) had stated:

> "For every million women alive in the United States, Canada, Europe today, about a 110,000 of those women will get breast cancer. This is obviously a tremendous public health issue. Of those 110,000 women get breast cancer, maybe several thousand of them are related to the total intake of exogenous oestrogens from every source, including eggs, meat, phyto-oestrogens, fungal oestrogens, the whole body burden of exogenous oestrogens. And by my estimates one of those 110,000 would come from eating meat containing oestrogens as a growth promoter, if used as prescribed."

However, the Appellate Body in 1998 denied evidentiary value to Dr. Lucier's statement for the reason that his opinion "… does not purport to be the result of scientific studies carried out by him or under his supervision focusing specifically on residues of hormones in meat from cattle fattened with such hormones …". (at para. 198 of the 1998 Appellate Body report)

In this case, Dr. Boisseau has explicitly admitted that he has never carried any experiments on hormones and has published no scientific paper, and the same applies for Dr. Boobis who does not appear to have any publication on hormones either.

Q18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol-17β is genotoxic. Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see paras. 118-119 of EC Rebuttal Submission (US case), paras. 123-124 of EC Rebuttal Submission (Canada case), paras. 87-91 and 153-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission, and paras. 90-97 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with the statements by Dr. Guttenplan and Dr. Cogliano. The evidence both *in vitro* and *in vivo* was already strong at the time of adopting the EC Directive and it is even stronger now establishing the direct genotoxic action of oestradiol-17β. In support of Dr. Guttenplan's statement that the evidence for the genotoxicity of estradiol is now stronger, see *New Eng. J. Med., 354, 270-282, 2006.*

The question is not whether the European Communities has established that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans, but whether the US and Canada have demonstrated to the requisite standard of proof that this adverse effect would not occur. They both assume (as does JECFA) that it will not occur, but they have failed to prove it, as has correctly been pointed out by Dr. Cogliano. As mentioned above, in the ACI rat model, the catechol estrogens did not cause mammary tumors; however, estradiol did cause such tumors in a dose-dependent response. Assuming greater bioavailability of estradiol and the fact that its oxidative metabolism to catechols and quinones occurs in various tissues as documented by their detection, the conclusion stated by Dr. Guttenplan that their absence in meat does not imply that meat from estrogen-treated cattle is without risk is correct.

The statement by Dr. Boisseau is beside the point, since the argument is hardly convincing that in 1999 JECFA established for the first time an ADI "in order to present in a more convincing way the outcome of its assessment". There is no trace of such an argument in the 1999 JECFA report which, it should be recalled, had found for the first time that "oestradiol-17β has genotoxic potential" (this admission was not in its 1988 report). Equally, the statement by Dr. Boobis lacks conviction because it is cast in cautious/conditional terms ("some, if not all, of the genotoxicity observed in vitro *would be expected* to exhibit a threshold…"). Again, Dr. Boobis appears to disregard the fact that evidence *in vivo* existed at the time that showed the direct genotoxicity of oestradiol-17β, which is reported in the 1999 SCVPH assessment and in the EC submissions to this Panel.

Q19. The European Communities states that "...it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance". Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case),paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]

EC Comments

The European Communities agrees with the thrust of the statements by Dr. Cogliano and Dr. Guttenplan. Indeed, it is true that there is no reason to expect a threshold to exist for a genotoxic chemical. After all, whether cancer will occur as a result of genotoxicity or hormonal action is from the regulatory point of view less critical, as the end result is the same: human cancer. As Dr. Guttenplan has stated, although DNA repair can occur, it presumably is occurring at all doses and the fraction of DNA damage repaired probably does not change at physiological levels, because the repair enzymes are unlikely to be saturated. However, would it not also be true that if the rate of repair were constant, an increase in the rate of formation of DNA damage would result in an increase in the time a mutagenic lesion remained in DNA? If this were the case, then there would be an increased likelihood for mutation if cell proliferation were occurring.

The arguments of Dr. Boisseau and Dr. Boobis that there is "no good evidence" that oestradiol is genotoxic *in vivo* or that it causes cancer by a genotoxic mechanism are unfounded. There are also a number of papers showing *in vivo* genotoxicity, some of which are already mentioned in the 1999 SCVPH report. Moreover, there are a number of scientific papers linking clearly elevated levels of 17β-oestradiol and other estrogens, at specific timepoints during development, to increased cancer risk (e.g. Hilakivi-Clarke L., Cho E., Raygada M., Kenney N.: *Alterations in mammary gland*

development following neonatal exposure to estradiol, transforming growth factor alpha, and estrogen receptor antagonist ICI 182,780, in J. Cell Physiol. 1997 170:279-89). The levels of 17β-oestradiol in children are so low that Dr. Boisseau's statement cannot be accepted scientifically. In the EC's view, it is beyond doubt that there is a link between 17β-oestradiol exposure during development (pre- and post-natal) and the risk of breast cancer later in life and this is not only due to endogenous production.

Q20. In your view, how do the European Communities' conclusions above relate to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary"? To what extent, in your view, has JECFA's conclusion that oestradiol "has genotoxic potential" affected its recommendations on this hormone?

EC Comments

The European Communities notes that Dr. Boobis, after so many assumptions and hypothesis in his reasoning of which he offers no proof, arrives at the conclusion that:

> "… a modest incremental increase in oestradiol concentration from exogenous exposure (above the ADI) might conceivably perturb endocrine effects, depending on the physiological state. However, non-endocrine effects, such as genotoxicity, will depend on the circulating concentration of oestradiol and will not vary with physiological state. Hence, the natural variations in circulating oestradiol levels should have a much greater effect on any genotoxic response than the much more modest change that could arise from the hormone in meat from treated animals, at any conceivable level arising from its use as a growth promoter …".

This reply of Dr. Boobis is based on his more erroneous underlying assumptions that oestradiol-17β is not genotoxic, that there is a threshold for residues in meat from animals treated with this hormone for growth promotion purposes, and that the rate of endogenous production by prepubertal children is as stated in the JECFA report. If these assumptions are false, as the available scientific evidence clearly demonstrates, then Dr. Boobis' statement – which is already a qualified one - would make no sense.

In any case, for the information of Dr. Boisseau and Dr. Boobis, the European Communities recalls that in the 1997 WTO hormones panel report (i.e. the first hormones panel), the US, Canada and JECFA were arguing that oestradiol-17β is not genotoxic, and this had influenced the findings of the 1987 panel report on these hormones. Since then, as the European Communities has been consistently arguing, the genotoxicity of oestradiol-17β is no longer seriously disputed and has now for the first time been accepted and written in the 1999 JECFA report re-evaluating the three natural hormones. But JECFA was not at all sure whether the genotoxicity of oestradiol-17β is due to its receptor-mediated action or by other direct mechanisms, because it uses in its 1999 report the soft terms "the carcinogenicity of oestradiol-17β is *most probably* a result of its interaction with hormonal receptors" (emphasis added). This contrasts sharply with the more affirmative and assertive statements to the contrary by both Dr. Boisseau and Dr. Boobis, who, by the way, have not done any direct experiments on these hormones in their professional life and so lack specific expertise.

More importantly, as the Appellate Body has held in the 1998 *Hormones* report:

> "… in most cases, responsible and representative governments tend to base their legislative and administrative measures on "mainstream" scientific opinion. In other cases, equally responsible and representative governments may act in good faith on the basis of what, at a given time, may be a divergent opinion coming from qualified

> and respected sources. By itself, this does not necessarily signal the absence of a reasonable relationship between the SPS measure and the risk assessment, especially where the risk involved is life-threatening in character and is perceived to constitute a clear and imminent threat to public health and safety…".

Indeed, in this case Dr. Boobis is basing his arguments on so many assumptions and hypothesis in order to arrive at the conclusion that oestradiol-17β is genotoxic only through its hormonal activity; but can Dr. Boobis provide the necessary assurance to the responsible risk management authorities of the EC that the residues of these hormones in meat from animals treated for growth promotion will not increase the risk of cancer? Furthermore, can Dr. Boobis clarify whether he believes that the evidence on which the EC based its risk assessment on genotoxicity of oestradiol does not come from "qualified and respected sources"?

It is also noteworthy that Dr. Boobis does not comment on other relevant evidence, for instance the fact that the US authorities also concluded for the first time in 2002 that "steroidal estrogens are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans, which indicates a causal relationship between exposure to steroidal estrogens and human cancer." For this reason, the US 2002 Report on Carcinogens (RoC) lists steroidal estrogens as known to be human carcinogens with the clarification that this listing now "supersedes the previous listing of specific estrogens in and applies to all chemicals of this steroid class." Moreover, in the same 2002 US Report it is stated that: "Veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food producing animals to above their normal levels."[8]

Dr. Boisseau and Dr. Boobis consider the assessments of JECFA as the Bible, although they know that the 1988 and the 1999 JECFA assessments are outdated by today's evidence and scientific standards. The European Communities has asked JECFA back in 1998 to withhold for a couple of years its assessment in order to take into account the new evidence which was then going to become available soon as a result of the studies that have been commissioned by the European Communities following the 1998 Appellate Body report in hormones. But JECFA for unknown reasons decided not to wait, despite the lack of any kind of urgency to review the three natural hormones in 1999. The European Communities hopes that JECFA will carry soon another assessment of these hormones on the basis of the most recent evidence available.

The European Communities agrees with the statements of Dr. Cogliano and Dr. Guttenplan. Indeed, the European Communities is arguing that a threshold cannot be established for the incremental human exposures that would be found in meat residues because there can be no assurance – and the US, Canada and JECFA did not provide one - that these additional exposures may not increase cancer risk, especially for the most sensitive parts of the population (prepubertal children), taking also into account the other identified areas of concern, such as developmental effects.

Q21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential? Does your answer depend on whether good veterinary practices are followed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see, *inter alia*, the SCVPH Opinions and paras. 63, 83, 89-91 and 93 of US First Submission, paras. 131-136 of Canada Rebuttal Submission]

EC Comments

[8] Available at http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540.

The European Communities is puzzled by the dismissive statements by Dr. Boisseau and Dr. Boobis. It is noteworthy that the 1999 JECFA report, on which they so much rely, states that *"… equivocal results have been reported for the induction of single-strand DNA breaks and DNA adducts have been seen in vivo and in vitro in some studies…*" (see WHO, technical series report no 893, at page 61). Because it is said that progesterone is not found to be mutagenic, JECFA concluded that "*on balance, progesterone has no genotoxic potential*" (emphasis added). It is recalled that no such statement was available in the 1988 JECFA evaluation report on this hormone. So, unlike Dr. Boisseau and Dr. Boobis, JECFA was more prudent when rejecting the genotoxicity of progesterone in 1999. Since then, more evidence has become available, as explained in the submissions of the European Communities, which increases the likelihood of possible genotoxic effects of progesterone and the other hormones. The 1999, 2000 and 2002 risk assessment by the SCVPH provide enough evidence to demonstrate that genotoxicity and other adverse effects from these hormones are possible and that there are a number of uncertainties surrounding their mechanism of action to warrant further investigation. As Dr. Guttenplan states, their genotoxic potential may be weak but cannot be excluded. In particular, the evidence available to the US, Canada and JECFA on the basis of which these hormones were authorised for animal growth promotion purposes, which dates in most of these hormones since the 1970s, is today not complete nor adequate to respond, with the required degree of certainty, to the gaps in our scientific knowledge which have been clearly identified in the 1999 and 2002 evaluations by the SCVPH. It should also be recalled that the European Communities did not permanently prohibit these hormones as proven carcinogens, as it did with regard to oestradiol 17β, but on a provisional basis taking into account the numerous and serious gaps in our scientific knowledge which have been clearly identified in the SCVPH assessments. The relevant question therefore is whether these two scientists, who – it should be recalled have no specific expertise on hormones - contest that there exists at least some uncertainty regarding the genotoxicity and other possible risks from the residues of these hormones in meat that have been identified by the SCVPH?

As regards the respect or not of good veterinary practice, the increased presence of these hormones in meat from cattle presumably treated with preparations containing these hormones has the potential to affect the hormone levels, in particular in infants and prepubertal children, whose levels of serum are much lower than those used by JECFA, as the more sensitive RCBA assays now demonstrate.

Q22. How would you define *in vivo* DNA repair mechanisms? How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat? Does your answer depend on whether good veterinary practices are followed in the administration of these hormones? To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones? Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why? [see para. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission].

EC Comments

Dr. Boobis's reply summarises more or less accurately the difficulties authorities face with genotoxic substances by stating that: "…A major difficulty in the risk assessment of such compounds however, is the identification of the threshold for such effects. This is because they occur with low incidence, and experimental studies do not have the statistical power to determine the location of the threshold with any confidence. Thus, whilst recognizing the likelihood for a threshold for even genotoxic effects the risk assessor is faced with the impossibility of locating it. The conservative solution is to assume that the response is linear and that there is no dose below which exposure is safe." (references omitted) Dr. Boobis then goes on to deny direct genotoxic potential to residues in meat from these hormones. However, if his underlying assumptions concerning lack of direct genotoxicity are false,

i.e. that oestradiol-17β is genotoxic and that there is no threshold for residues in meat from animals treated with this hormone for growth promotion purposes and that the rate of endogenous production by prepubertal children are much lower than those stated in the JECFA report, then Dr. Boobis should accept that DNA repair mechanisms are not sufficient to eliminate DNA damage.

Moreover, Dr. Boobis and Dr. Guttenplan appear to miss another important point. If the rate of repair were constant, an increase in the rate of formation of DNA damage would result in an increase in the time a mutagenic lesion remained in DNA. If this is the case, then there would be an increased likelihood for mutation if cell proliferation were occurring. Dr. Guttenplan states that "…most DNA damage by any agent is repaired and there is considerable redundancy in DNA repair, insuring that repair is effective. However, a small fraction of damage inevitably escapes repair …". The implication of this should be that the unrepaired fraction would be increased with an increase in the rate of damage formation resulting from increased exposure to estradiol and the resulting estrogen genotoxic metabolites. In other words, a higher rate of damage may be accompanied by an increased fraction of unrepaired potentially mutagenic lesions.

The European Communities notes also the interesting statements by Dr. Guttenplan that "… there is no reason to assume that DNA repair processes involved in DNA damage produced by estrogen metabolites are any more or less effective than those involved in repair of other carcinogens …", and that "… since it is not likely to be different for estrogen derived damage than other types of damage it is not really relevant [if this is not examined in detail by the SCVPH]. There is some evidence referred to in the SCVPH Opinions that error-prone DNA repair of certain estrogen derived damage can occur."

Q23. To what extent is it necessary or possible to take into account the "long latency period" of cancer in the conduct of a risk assessment, which is supposed to assess carcinogenic effects of these hormones when consumed in meat? Have the hormones in dispute been used as growth promoters over a sufficient number of years for an assessment of their long-term effects on human health to be made? [see para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case)].

EC Comments

The European Communities notes the different and partly contradictory replies of the experts. It agrees, however, with Dr. Cogliano and Dr. Guttenplan that a sufficiently long latency period (at least 20 years) is extremely important. However, it is also true that such epidemiological studies will not be able to discriminate (or separate out) the true origin of cancer because of so many co-founding factors. This is admitted by both Dr. Boisseau and Dr. Boobis, thus undermining the position of the US and Canada that these hormones have been in use for a long time to be able to rule out their carcinogenic effects on humans. And Dr. Boobis concludes by stating that "…Hence, a negative result from such an observational study would not resolve the issue." However, the European Communities would recall the evidence cited in the 1999 SCVPH report – coming from the studies published by the IARC – showing that the frequency of breast cancer in countries where hormones are allowed is higher compared with countries where the hormones have not been used. Thus, this is just an indication that there might be a link between consumption of red meat and breast cancer.

Q24. To what extent is it possible to identify possible confounding factors causing cancer and attribute them to identified sources? What are the implications of these factors for the conduct of a risk assessment evaluating the adverse affects caused by residues of growth promoting hormones in meat? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

EC Comments

The European Communities notes that the replies of all the scientists substantially agree with the EC position and the reasons for which it was not possible to carry out such an epidemiological study after the 1998 Appellate Body report in the hormones case. Moreover, their replies also undermine indirectly the position of the US and Canada that these hormones have been in use for a long time to be able to identify and, hence, rule out their carcinogenic effects on humans. However, the European Communities would recall the evidence cited in the 1999 SCVPH report – coming from the studies published by the IARC – showing that the frequency of breast cancer in countries where hormones are allowed is higher compared with countries where the hormones have not been used. This is of course no conclusive proof, but just an indication sufficient to raise concerns about the gaps of our knowledge in this area.

Q25. To what extent do the three recent studies referred to by the European Communities confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones? Please also comment on the EC statement that one of the studies "was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, which means that the subjects should have been exposed to hormone-free meat in their diet. This may further imply that it cannot be excluded that the risk of cancer may be further increased if meat treated with hormones for animal growth promotion were to be consumed". [see paras. 145-148 of EC Rebuttal Submission (US case) and paras. 139-142 of EC Rebuttal Submission (Canada case), footnote 97 in para. 147 of EC Rebuttal Submission (US case), and Exhibits EC-71,72,73]

EC Comments

The European Communities notes the different and partly contradictory views expressed by the experts. Dr. Boobis dismisses the relevance of the studies cited by the European Communities for reasons that have to do essentially with what he calls the "weight of the evidence" approach. But as the European Communities explained before, this approach is not appropriate nor is it required under the *SPS Agreement*. It appears that Dr. Boobis' strongly held views - which it is worth recalling do not come from specific research he has conducted himself on these hormones - would only change if the evidence produced by the European Communities "confirms a risk to human health". Dr. Boobis is apparently not restrained in displaying such strongly held views, despite the fact that JECFA's evaluation is based on data from the 1970s – 1980s, when the experiments conducted by the industry then seeking regulatory approval in the US did not comply either with the kind of criticism now levelled by Dr. Boobis against the more recent evidence produced by the European Communities. In other words, Dr. Boobis is now demanding evidence of positive proof of harm, which the applicant pharmaceutical industry did not disprove (i.e. the lack of possible harm) with the data it submitted for regulatory approval in the 1970s and 1980s in the US.

Dr. Boobis apparently feels no restrain as an expert to state that: "*as long as exposure does not consistently exceed the ADI, there should be no appreciable risk to human health*." But this is both speculative and unspecific. What is an appreciable risk? How do we interpret the qualitative term "no appreciable risk"? Is it 1% or 10% or some other value? And why would a scientific expert, who is supposed to do only a risk assessment, decide what is "appreciable" risk, a task reserved normally for the risk manager? Is it not normally the task of a scientific expert in a risk assessment exercise to explain the scientific evidence and see if there is scientific uncertainty? How confident can Dr. Boobis be when stating that: "However, as indicated elsewhere in my responses, the evidence is against an increased risk from such exposures". Would Dr. Boobis accept that there is some uncertainty surrounding his statements rejecting an increased risk of cancer from the residues of these hormones in meat? And would Dr. Boobis contest that the evidence with which he does not agree comes from reliable and credible sources?

Another example of the "absolutist" approach by Dr. Boobis is his comment on the EC epidemiological study making a correlation between meat consumption and colorectal cancer, showing an increased frequency in the US and Australia compared to Europe. But he dismisses these results because he relates the lower risk observed in Europe by linking it with a lower meat consumption in Europe. However, the numbers showing a lower frequency of colorectal cancer is only from Northern Europe, whereas the data for meat consumption is for all European countries combined. If so, would Dr. Boobis accept that this data might indicate that some uncertainty exists concerning the alleged by the US and Canada safety of hormone residues in meat treated for animal growth promotion?

The European Communities agrees with the comments of Dr. Cogliano, who rightly summarises the issues at stake. The European Communities also agrees with the careful and scientifically sound statement by Dr. Guttenplan concerning the study by *Liu S and Lin YC (2004)*, in that their "... observation was not previously reported …" and that "… the study does suggest that additional tests of zeranol should be carried out." Consequently, the relevant legal question is who is to conduct these additional experiments and what should the regulatory regime be until their results become available? One of provisionally prohibiting or one of allowing the use of these hormones for growth promotion purposes?

Q26. Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91]

EC Comments

The European Communities notes the different views expressed by the experts. What is important, however, is that there appears to be some consensus for the proposition – nicely summarised by Dr. Cogliano – that: "*… it is possible that differences in exposure to exogenous hormones can be one cause, but the data are not sufficiently specific to establish a link between these observations*." Indeed, Dr. Boobis also states that: "*There is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans. There are some studies that are consistent with such an association, but there are several other possible explanations for the findings, some of which are more plausible than hormones in meat as being causal.*." (emphasis added). And Dr. Guttenplan states that: "… *However, the results are at least consistent with a possible effect of hormones on breast and prostate cancer* ...".

As already explained above, their replies undermine indirectly the position of the US and Canada that these hormones have been in use for a long time to be able to identify and, hence, rule out their carcinogenic effects on humans. It should also be pointed out that the European Communities cited this epidemiological evidence in the 1999 SCVPH not as an affirmative or adequate proof but just as an indication and possible explanation. In this sense, the three experts appear to agree, although at varying degrees. Furthermore, the plausibility of the EC argument is slightly reinforced by the fact that the differences in the cancer rates observed in the European Communities and US go in the expected direction in case of an effect, with higher rates in places where hormone-treated meat is consumed; and, similarly, the study of time trends is in agreement with the use patterns of these products in animal production. Again, the European Communities advanced this argument to demonstrate that the scientific uncertainty is growing concerning the harmless nature of the residues

of these hormones in meat and to counter the arguments of the US and Canada that there is no uncertainty surrounding the safety of residues of these hormones.

(b) Residue analysis

Q27. How do the residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue?

EC Comments

The European Communities wishes to stress that the difference in the residues is not only structural/chemical but also qualitative and quantitative. For instance, one of the studies by the EC (Stephany 2001, APMIS 109, 357-364) (see exhibits EC-49 and EC-19) gives some data on residues in meat samples from the US market. In the so called "HQ clean HFC US beef" study (i.e. hormone-free meat), an average 0.004 ppb of estradiol was found, whereas in the so called "M/LQ domestic US beef" study (i.e. hormone-treated beef) an average of 0.030 ppb estradiol was present. So this study indicates that the consumption of meat from the regular US market contains *7.5 times more estrogens than in meat from untreated cattle.* This is important and completely different information from that provided in the data from the controlled studies which were conducted in the 1960s, 1970s and 1980s by the pharmaceutical industry for the purpose of seeking authorisation of these hormones in the US and Canada (and on which JECFA based its evaluations in 1988 and in 1999).

Q28. How do the hormones naturally present in animals, meat, or human beings differ from the residues in meat of the three natural hormones used for growth promotion purposes?

EC Comments

The European Communities would note that the statement by Dr. Boisseau is partially incomplete and partially false. First, no estradiol-alpha is produced endogenously by humans, whereas this is the main residue in the target tissue (liver) in cattle treated with oestradiol 17β. This metabolite, when ingested by humans, is highly susceptible to give catechols in target organs (colon, liver) which may react with nucleophilic compounds and induce some disruptions. Moreover, the hormonal effect of estradiol-esters which are found as residues in treated cattle are not examined in the old data submitted by the pharmaceutical industry for the approval of this hormone, despite the fact that we know that they are orally active and probably partially absorbed in the intestine lymph circulation.

The European Communities considers the statement by Dr. De Brabander very informative, in particular the statements the three natural hormones used for growth promotion purposes are synthetised (prepared) from plant material and that in plant material the $^{13}C/^{12}C$ ratio is different from the $^{13}C/^{12}C$ ratio of animals. Equally, the finding that the residues of the endogenously produced natural hormones in cattle are in the 17α form (inactive) while the use of the natural hormones for growth promotion purposes may lead to residues in the ß form (active form). The first of these remarks may provide a better understanding to the simplistic argument made by the US and Canada that humans are exposed to much higher burdens of residues from these hormones when eating natural products (e.g. broccoli) and they should not worry about the little increment they receive from eating meat treated with these hormones for animal growth promotion purposes.

Q29. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the synthetic hormones found in meat in their assessment of the risks from such residues? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? How do they compare with the MRLs set by Codex? [see paras. 165-176 of EC Rebuttal Submission (US case); pages 55-68 of the Opinion of the SCVPH

of 30 April 1999 in US Exhibit 4, para. 144 of US First Submission, Exhibits US-6 and 7, footnote 46 of US Rebuttal Submission]

EC Comments

The European Communities considers that the statement of Dr. Boisseau is incorrect because the 1999 opinion of the SCVPH was structured in two levels: one making the analysis stated by Dr. Boisseau, but also a second one where an exposure assessment was nevertheless made to residues of the synthetic hormones (trenbolone, zeranol and MGA) in meat, in particular to underscore the point that the ADIs fixed by JECFA are most likely to be exceeded as regards specifically prepubertal children, taking into account their low levels of endogenous production. Specific reference can be made to paras. 165-176 of the EC's rebuttal submission and to the clearly marked sections of the 1999 SCVPH opinion. The European Communities not only considered the ADIs and MRLs set by JECFA but went even further and examined the tolerance levels recommended by the USA. Moreover, it is obvious, even from a cursory look at the 1999 and 2002 SCVPH opinions, as well as from the Exhibits EC-65, 67, 68, 69, 70 and 73, that the European Communities did examine the consequences from observance or lack thereof of GVP.

The statement by Dr. De Brabander confirms the EC argument that the data used by JECFA are not only too old but have also been obtained with methods that are no longer reliable today. This may also explain why the parties and JECFA have so strongly refused to provide those data to the European Communities and the Panel.

Q30. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the three natural hormones in meat in their assessment of the risks from such residues? Is it possible to compare these to the ADIs recommended by JECFA in 1999? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? [see paras. 120-123 and 155-164 of EC Rebuttal Submission (US case), pages 33-54 of 1999 Opinion in Exhibit US-4, para. 144 of US First Submission, and 52nd JECFA Report in Exhibit US-5]

EC Comments

For the reasons already explained above regarding the synthetic hormones, the European Communities considers that the statement of Dr. Boisseau is also incorrect as regards the three natural hormones. Specific reference can be made to paras. 155-164 of the EC's rebuttal submission and to the clearly marked sections of the 1999 SCVPH opinion. The European Communities not only considered the ADIs and MRLs set by JECFA but went even further and examined the acceptable levels and tolerances recommended by the USA. Moreover, it is obvious, even from a cursory look at the 1999 and 2002 SCVPH opinions, as well as from the exhibits EC-65, 67, 68, 69, 70 and 73, that the European Communities did examine the consequences from observance or lack thereof of GVP.

The European Communities considers that the statement by Dr. Boobis is clearly wrong. In section 4.1.5 of the 1999 opinion, the SCVPH made a detailed exposure assessment both for the ADI established by JECFA and the acceptable levels and tolerance recommended by the US authorities. It is recalled that JECFA did not recommend MRLs for the different types of tissue, while the US has identified acceptable levels. Therefore, for comparative purposes and in order to be exhaustive, the SCVPH had to apply conversion rates. The result was that the ADI recommended by JECFA (0-50 ng/kg bw/day) is lower than that recommended by the US (102 ng/kg), as calculated by the SCVPH on the basis of the acceptable levels for individual tissues. However, both the JECFA and the US values are based on endogenous production by prepubertal children that the SCVPH found to be too high.

As the SCVPH found that the US acceptable levels and recommended tolerance will be exceeded by about 1,700 fold times, it was obvious that the JECFA ADI, which is lower than the recommended US tolerance, will also be necessarily exceeded. The SCVPH exposure assessment is made for prepubertal children, as the most sensitive part of the population. Moreover, the data used in section 4.1.5 of the 1999 SCVPH report are based on residue values that are assumed to result from administration of these hormones that respects use as authorised in the US ("GVP"). Indeed, Table A3 attached as Annex to the 1999 opinion uses the TMDI from the 1999 JECFA report. There is another section in the 1999 SCVPH opinion (section 3.3), which discussed the higher residue values that will result inevitably from misuse and abuse. It should also be added, that the same methodology and reasoning was applied for the other 2 natural hormones.

While it is admitted that an exposure assessment on natural hormones is a difficult task that has to cope with many uncertainties and may therefore not be as straightforward as desired, Dr. Boobis opinion that the European Communities did not carry out an appropriate exposure assessment is clearly not justified.

Q31. Please comment on the US statement that "concentrations of oestradiol-17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of oestradiol-17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." In your reply please take into account the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels" and the statement by the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered. [see paras. 51 and 144 of US First Submission and Exhibits US-6 and 7, para. 98 of EC Replies to Panel Questions, Exhibit EC-101, and paras. 2.3.2.3 of the 1999 Report of SCVPH]

EC Comments

The European Communities considers that Dr. Boisseau's reply accepts the US statement without much questioning. However, in the US statement there exist phrases which are imprecise and possibly misleading, such a "… do not vary significantly …", "… well within the physiological range …", "… may be slightly higher …". Neither the US nor Dr. Boisseau explain what is significant or what is the physiological range, as we know that the values for these concepts can vary substantially. For example, as explained by Dr. De Brabander in his reply to question no 27, one of the studies conducted by the European Communities indicates that the consumption of meat from the regular hormone treated meat market in the US contains 7.5 times more estrogens than in meat from untreated cattle. Moreover, Dr. Boisseau did not comment on the part of the question relating to the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels." Indeed, in this 11th US report the terms "can increase estrogens in tissues of food producing animals to above their normal levels" do not explain by how much above their normal levels – supposing one could define such normal levels – could such an increase be. These issues are not unimportant, as the earlier comments of the European Communities on the absence of a threshold have demonstrated. Given the much lower levels of endogenous production of these hormones by prepubertal children, the European Communities considers that the reply by Dr. De Brabander rightly points out the increased risk which repetitive exposure to such higher residues can present to the most sensitive parts of the population.

Q32. Please comment on the conclusions of the EC risk assessment (Opinion of the SCVPH of April 2002) that ultra sensitive methods to detect residues of hormones in animal tissues have become available but need further validation. What is the significance of this with regard to identifying whether the natural hormones in meat are endogenously produced or are residues of hormones used for growth promotion purposes?

EC Comments

The reply by Dr. Boisseau is scientifically unsound. As is very well explained by Dr. De Brabander's statement, there is an urgent need to apply the latest analytical methods to determine the nature and level of the residues from these hormones and all their metabolites, in view of the widespread use of meat and meat products. Moreover, precisely because of the endogenous production of the three natural hormones, it is imperative that the analytical method used should be able to determine accurately the true origin of residues in meat and their magnitude (i.e. endogenous or exogenous source).

Q33. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

EC Comments

The European Communities notes the conflicting replies of Dr. Boisseau and Dr. Boobis on the reasons for which JECFA decided to evaluate the three natural hormones in 1999 and on the significance of the establishment of ADIs for the first time.

The European Communities notes also the reply of Dr. Boisseau that the data on residues used in 1999 where the same as those used in 1988, in other words dated from the 1970s. As Dr. De Brabander correctly explains, these data should no longer be considered to be credible and reliable. It is therefore imperative that JECFA discloses to this Panel and the public the residues data it used in 1999 in order to verify in an open and objective manner the credibility and validity of its conclusion on the existence of a threshold, the lack of genotoxicity, etc.

Dr. Boobis admits that the 1988 evaluation was made by JECFA even without toxicological monographs, which means, *inter alia*, that for the two synthetic hormones – trenbolone acetate and zeranol – which have not been evaluated since 1988, JECFA's conclusions are no longer reliable. Moreover, Dr. Boobis accepts that: "…in the intervening time from the first to the second evaluation, it became clear that exposure to the natural hormones, albeit at levels appreciable higher that found in meat from treated cattle, could have adverse effects in humans. Hence, the implicit conclusion was that it was necessary to establish ADIs, to serve as health based guidance values. These could then be used as a benchmark for comparison with exposure via the diet." It is therefore remarkable that in the end JECFA did not recommend MRLs.

Q34. Please comment on the EC argument that the 1999 JECFA report based its findings on (a) outdated residues data and (b) not on evidence from residues in meat but on studies with experimental animals and on general studies of IARC. If the data were not new, did JECFA take this into account in its evaluation? What are the implications of using such data for the

purpose of conducting a risk assessment? How reliable are extrapolations from animal studies to possible adverse effects on humans? How does this compare with the kind of data and studies used with respect to other veterinary drugs? [see para. 120 of EC Rebuttal Submission (US case), para. 102 of EC Rebuttal (Canada case)]

EC Comments

The European Communities notes that both Dr. Boisseau and Dr. De Brabander agree in that the data used by JECFA in 1999 are old (since well before 1987). Dr. Boisseau usefully clarifies that some of them have even not been published in peer-reviewed scientific journals, as has been consistently arguing the European Communities in these proceedings. However, the argument advanced by Dr. Boisseau to minimise the importance of their old nature is not scientifically sound. For example, Dr. Boisseau does not explain how would it be possible to integrate in the risk assessment procedure conducted by JECFA in 1999 the residues of estradiol-esters and estradiol-alpha given that their specific hormonal or metabolic characteristics were not examined at all in the 1988 data? Moreover, concerning estradiol-alpha, which is the main metabolite found in target tissue (liver) of treated cattle and which we know that it will be metabolised in catechol derivatives, no specific evaluation of this genotoxic mechanism of action has been performed by JECFA. Against this background, is it possible for Dr. Boisseau that the quality of the data used by JECFA in 1999 was scientifically credible?

As has been explained above, on the critical questions of genotoxicity and the existence of a threshold, the level of endogenous production of the natural hormones by pre-pubertal children, etc., JECFA's evaluation hinged on a number of instances "on the balance" of the evidence (e.g. on the genotoxicity of oestradiol, progesterone, zeranol, etc.). Can Dr. Boisseau provide an assurance to the European Communities that JECFA's conclusions would have not been different if more recent and accurate data were available to it?

Q35. Please comment on the European Communities claim that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. Is this correct? Have subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies? [see para. 171 of EC Rebuttal Submission (US case), para. 161 of EC Rebuttal Submission (Canada case), para. 55, including footnote 60 of US First Submission and Exhibits CDA-20, 33, 34, and 35]

EC Comments

The European Communities notes that both Dr. Boisseau and Dr. De Brabander agree in that the data used in 2000 by JECFA for MGA date from the 1960s and 1970s. The explanation offered by Dr. Boisseau is not valid for basic the same reasons as those stated in its comment to the previous question. For instance, the "low-dose" issue was not recognised in peer-reviewed literature before the mid 90s. Thus, all the research into possible low-dose effects has not been considered in the 2000 JECFA report. In the light of the new evidence provided by the European Communities in its risk assessment of 1999, 2000 and 2002, showing so many gaps and uncertainties in our knowledge on MGA, can Dr. Boisseau assure the Panel that all the relevant and necessary scientific aspects about the safety of MGA have been completely and properly analysed and assessed or is it rather fair to say that there is a need for further research because of scientific uncertainties?

(c) Dose-response relationship

Q36. How would you describe a dose-response assessment? Is it, as suggested by Canada in para. 78 of its Rebuttal Submission, "widely, if not universally, accepted that adverse effects arising from hormonal activities are dose-dependent"? Is dose-response assessment a necessary component of hazard characterization? Or, is there an alternative approach which can replace

the dose-response assessment. Is a dose-response assessment feasible/necessary for substances that are found to be genotoxic or to have genotoxic potential? [see para. 153 of EC Replies to Panel Questions, para. 200 of EC Rebuttal Submission (US case); paras. 143, 154, and 156 of US First Submission, paras. 70-74 of US Replies to Panel Questions, and paras. 34 and 37-40 of US Rebuttal Submission; paras. 76-82 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with Dr. Cogliano's statement that "dose-response assessment is not a necessary component of hazard characterization." This is also consistent with the Appellate Body's 1998 decision in the *Hormones* case that a qualitative assessment of the risk is acceptable under the SPS Agreement. The European Communities also notes that Dr. Boobis accepts that "in Europe and generally within JECFA, once a compound is identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action, no exposure is considered without risk…". The European Communities also notes that the approach for such compounds that are known or assumed to exhibit no threshold in their dose-response curve, varies from one region to another, and this possibly explains the sharp difference between the parties to this dispute. What is also important to note is that there exist no internationally agreed guidelines on this issue, in the sense of Article 5.1 of the *SPS Agreement*. In the light of Dr. Boobis reply, the fact that the US and Canada have been arguing, on the basis of experience derived from their domestic practice, that the European Communities did not perform a dose-response assessment in this case is not really relevant.

Q37. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

EC Comments

The European Communities notes that Canada's argument that "…a dose-response assessment should *always* be conducted for chemical agents…" is not a scientifically sound nor a legally binding proposition. Both Dr. Boisseau and Dr. Boobis appear to agree with the EC argument contesting Canada's proposition. Furthermore, Dr. Boobis states that JECFA may consider a dose-response unnecessary for genotoxic substances, although this – in his view- "is a very unlikely occurrence for a veterinary drug because, in general, producers tend to screen out genotoxic compounds during the development process." However, Dr. Boobis does not probably take into account the fact that the hormones at issue have been approved in the US and Canada in the 1970s and since then the pharmaceutical industry did not carry out any kind of screening and did not generate new set of genotoxicity data.

(d) Sensitive populations

Q38. Please describe the range of physiological (or background) levels of the sex hormones in humans and identify the variations in these levels on the basis of age, sex group, and physiological stages.

EC Comments

The European Communities notes that Dr. Boisseau does not appear to contest the values stated in the SCVPH but rather whether the assays have been properly validated. However, it is not very uncommon in JECFA to use data from assays which are not yet properly validated. The European

Communities believes that the values from JECFA for serum 17β-oestradiol levels in prepubertal children are not correct. JECFA originally used the limit-of-detection as the "real" level when they could not measure the levels (or find it in the old literature as explained earlier). JECFA apparently questions the very low values determined by Klein et al., 1994, and Dr. Boobis suggest using "newer data from Klein (Klein et al., 1998)". However, Klein et al., 1998 only reports values for girls with precocious puberty, while they in the paper still refers to the original data (Klein et al., 1994) for the levels in normal prepubertal girls.

Dr. Boobis also writes that the values from another ultra sensitive bioassay (Paris et al., 2002) suggest that the levels are significantly higher, however, that assay measures estradiol equivalents (includes other natural estrogens and anything that may interact with the estrogen receptor). Nevertheless, even if the values from Paris et al., 2002 are used, they are still less than 1/3 the values shown in the table. Dr. Boisseau and Dr. Boobis ask if the bioassays have been properly validated. However, JECFA used the limit-of-detection when it could not measure the real values, which is clearly not acceptable! The real values for serum 17β-oestradiol in prepubertal children still remain to be properly documented. Since it is not possible to make the calculation on daily production rates without knowing the serum levels and the metabolic clearance rate in the most sensitive segment (children), and JECFA considers such data essential for determining an ADI, it must be accepted that JECFA cannot set the ADI and MRL before the values are known!

Q39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol-17β and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the populations which have been identified as particularly sensitive such as prepubertal children" [see para. 147 of the EC Replies to Panel Questions]

EC Comments

The European Communities notes that the replies of Dr. Boisseau conflict with those of Dr. Sippel. The European Communities agrees with Dr. Sippel's assessment, who demonstrates why there are a number of sources confirming the values mentioned by Klein et al, 1994 and 1999. Dr. Boisseau's reply is also false, because the SCVPH has performed – unlike JECFA which based its assessment on data from 1974 - the quantitative assessment taking account the lower endogenous production levels for pre-pubertal children from the most recent and reliable data (see also comments on previous question).

Q40. The European Communities states that "the levels of endogenous production of the hormones by prepubertal children is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship ..." Please comment on the methodology used by the SCVPH to support the conclusion that hormone levels are lower than previously thought, and in particular comment on the validity of these methodologies and their conclusions. Would your conclusions have been the same at the time of adoption of the Directive in September 2003?

EC Comments

JECFA originally used the limit-of-detection as the "real" level when they could not measure the levels. Dr. Boobis suggest using "newer data from Klein (Klein et al., 1998)". However, Klein et al., 1998 only reports values for girls with precocious puberty, while they in the paper still refers to the original data (Klein et al., 1994) for the levels in normal pre-pubertal girls. Dr. Boobis also writes that the values from another ultra sensitive bioassay (Paris et al., 2002) suggest that the levels are significantly higher, however, that assay measures estradiol equivalents (includes other natural

estrogens and anything that may interact with the estrogen receptor). Nevertheless, even if the values from Paris et al., 2002 are used, they are still less than 1/3 of the JECFA values shown in the table. The real values for serum 17b-oestradiol in prepubertal children still remain to be properly documented, although Dr. Sippel provides convincing explanations and arguments to accept as valid the results from the RCBA assay.

Q41. Why would individuals with the lowest endogenous hormone levels be at greatest risk? How would the risks for these individuals arising from hormones naturally present in meat differ from the risks arising from the residues of hormone growth promoters?

EC Comments

The European Communities considers that the replies of the experts confirm the basic concerns in the 1999 SCVPH risk assessment about the need to protect the pre-pubertal children, and Dr. Sippel has summarised correctly the reasons. The replies by Dr. Boisseau and Dr. Boobis as to whether the risk would be the same or different are not entirely convincing. For instance, concerning estradiol-17-esters and estradiol-alpha found as residues in treated steers (Maume et al, APMIS 109 (2001) 32-38, Maume et al, Anal Chim Acta, 483 (2003) 289-297), it would not be true that the risks are the same. It is preferable to establish a rigorous risk assessment evaluation by considering specific classes of residues. The European Communities considers that the most important studies available provide a bioavailability rate which is 10% or higher (see the 2nd EC Written Submission).

Q42. To what extent, in your view, has JECFA taken into account the particular situation of sensitive populations, in particular prepubertal children, in its risk assessments with respect to oestradiol-17β? Please compare the original data concerning endogenous production of natural hormones by prepubertal children upon which JECFA based its assessment and those used by the European Communities in its risk assessment. In your view, does the scientific material referred to by the European Communities require a revision of the Codex recommendation with respect to oestradiol-17β? [For the questions in this section, see paras. 121-122 of EC Rebuttal Submission (US case), paras. 103-104 of EC Rebuttal Submission (Canada case), Exhibits EC-88, 99, para. 42-45 of US Rebuttal Submission, paras. 84 and 159 of US First Submission, and for JECFA's work Exhibits CDA-11, 16, 17, 18, 39]

EC Comments

The European Communities notes the replies of Dr. Boisseau and Dr. Boobis, who incidentally have not carried out any research themselves on these hormones and so have no specific expertise, are very monolithic and one-sided. Their views are based again on the assumptions that this hormone is not genotoxic and that the rate of endogenous production by prepubertal children is correctly cited in the JECFA report. But if an over-estimation of endogenous levels and production rates would exist, as the more recent evidence demonstrates, then a revision would be immediately necessary. And there are so many other reasons to believe that the JECFA evaluation is scientifically wrong, as explained above (old and unreliable data, etc.), no reliance can be placed on the replies by these two experts.

(e) Bioavailability

Q43. Please define bioavailability, comment on the significance of bioavailability to assessments of risk, and on the degree of bioavailability of the residues of the hormones at issue when consumed in meat, taking into account parties' differing views on this matter. [see paras. 123-124 of EC Rebuttal Submission (US case), para. 105-106 of EC Rebuttal Submission (Canada case), paras. 100, 155-159 of the EC Replies to Panel Questions, paras. 32 and 41-42 of US Rebuttal Submission, paras. 69, 71, 88-89 and 146 of US First Submission, and para. 134 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with the summary on this question as stated by Dr. Guttenplan. Indeed, Dr. Boisseau writes "oestradiol-17β is inactive orally". This is simply factually wrong! Oestradiol-17β is routinely administrated to humans as a powder or in the form of pills that are taken orally. For example, in the study reported by Lampit et al., 2002, the girls were administrated 8 µg conjugated oestradiol-17β in the form of encapsulated powder. Moreover, in the "benchmark study" on oestradiol-17β performed in rats (Cook et al., 1998) the rats were orally dosed with oestradiol-17β. Thus, there are no doubts that oestradiol-17β is orally active.[9] It is also not disputed that no rigorous procedure has been used to assess hormonal risk concerning estradiol-ester, in particular on absorption via the lymphatic route. It is clear that estradiol and estradiol-esters are not devoid of effect when given orally (Paris et al, APMIS, 2001).

The European Communities has provided credible recent evidence that the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account). Moreover, the calculations presented in the SCVPH assessment clearly that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children. As Dr. Guttenplan states, this would represent a risk factor. Neither Dr. Boisseau nor Dr. Boobis provide a specific reply to this other than repeating the general and hypothetical assumptions of JECFA that their bioavailability "is rather low". It should also be noted that the bioavailability of the three synthetic hormones has not been determined by JECFA.

(f) Good veterinary practice (GVP)

Q44. Please define "good veterinary practice" (GVP) and/or "good practice in the use of veterinary drugs" (GPVD). What are the relevant Codex standards, guidelines or recommendations relating to GVP/GPVD? Please comment on the statement by the European Communities that the definition of the GPVD is "circular and hence problematic." [see para. 88 of the EC Replies to Panel Questions]

EC Comments

The statement by Dr. Boisseau that "Codex did not adopt any guideline on GVP aimed at minimizing the occurrence of veterinary drug residues in animal derived food" confirms what the European Communities has always been arguing. The European Communities recalls that the Appellate Body in the 1998 *Hormones* decision has held that:

> "… We consider that the object and purpose of the SPS Agreement justify the examination and evaluation of all such risks for human health whatever their precise and immediate origin may be. We do not mean to suggest that risks arising from potential abuse in the administration of controlled substances and from control problems need to be, or should be, evaluated by risk assessors in each and every case. When and if risks of these types do in fact arise, risk assessors may examine and evaluate them. Clearly, the necessity or propriety of examination and evaluation of such risks would have to be addressed on a case-by-case basis. What, in our view, is a fundamental legal error is to exclude, on an a priori basis, any such risks from the scope of application of Articles 5.1 and 5.2 …". (at para. 206)

[9] See Cook J.C., Johnson L., O'Connor J.C., Biegel L.B., Krams C.H., Frame S.R., Hurtt M.E.: Effects of dietary 17 beta-estradiol exposure on serum hormone concentrations and testicular parameters in male Crl:CD BR rats, Toxicol Sci. 1998 44:155-68.

The European Communities also recalls that the inspections and measurements of hormone residues in US meat made by the European Communities revealed that hormones were found in what was supposed to be a "guaranteed hormone-free beef", and that the levels of one of the hormones (MGA) were too high to be achieved by the legal dosing. The European Communities has also performed two specific risk assessments for the US and Canada that comply with the requirements laid down in para. 206 of the Appellate Body report mentioned above (see in particular EC exhibits 67-73). Thus, there is specific evidence proving that GVP is not followed by at least by some meat producers in the US and Canada. The debate on this issue demonstrates, as Dr. De Brabander shows, that there is an important difference between the theoretical assumption of respecting GVP and real life.

Q45. In conducting a risk assessment of specific veterinary drugs, what assumptions are made concerning GVP, if any? How, if at all, are risks that might arise from the failure to follow good veterinary practice in the administration of veterinary drugs addressed?

EC Comments

As Dr. Boisseau states, the Codex recommendations (whether ADIs or MRLs) "are only meaningful in countries where GVP are effectively implemented." There is, however, plenty and undisputed evidence that frequently GVP is not respected in the US and Canada (although Canada appears to have a slightly better record). However, as Dr. De Brabander rightly explains, the argument of Dr. Boisseau is not correct that risk assessors cannot take into account possible misuse or abuse in their assessment, as the 1999 and 2002 SCVPH opinions have clearly demonstrated and as Dr. Boobis also admits in his reply to question no 46.

Q46. To what extent were risks from misuse or abuse assessed by JECFA in its evaluation of the hormones at issue? In terms of the three synthetic hormones at issue, how is GVP relevant to the establishment of MRLs by JECFA?

EC Comments

Although the theoretical description by Dr. Boobis is more or less accurate, the important point is that the pharmaceutical industry did not carry out any systematic experiments on possible misuse or abuse of these hormones nor did it submit such data to the US and Canadian regulatory authorities in the 1970 and 1980s when applied for the authorisation of these substances. The result is that also JECFA, which based its evaluation on the same old data, did not consider systematically the issue of possible misuse or abuse. This is a fundamental flaw in JECFA's assessment of these hormones.

As the European Communities has already explained, even the US authorities now accept (see e.g. the 2002 US Carcinogenesis Report) that the administration of these hormones to cattle, which presumably respects GVP, leads to residue levels that exceed the levels from endogenous production. This means that when misuse or abuse occurs the excess levels are inevitably going to be much higher. According to the studies cited by the European Communities, e.g. Exhibits EC-12 and 17 and 73, the level of residues in case of misuse or abuse by far exceed the ADIs recommended by JECFA and the acceptable levels and tolerances recommended in the US and Canada.

Q47. How significant are any differences in GVP in the European Communities, the United States, and Canada? Does the EC risk assessment take into account relevant control mechanisms with respect to GVP in place in the United States and/or Canada? If so, what are their conclusions?

EC Comments

The statement of Dr. Boisseau is partly false. The European Communities has carried out a specific assessment of the US and Canadian situation concerning respect of GVP (see EC Exhibits 67 and 68) and has taken into account the multiple sources of misuse and abuse that frequently occur there (see EC Exhibits 69 -70, and 71-72, 96, and 102-103). As Dr. Boisseau states these hormones are sold over the counter in the US and Canada, which means that there is in reality no way to control their possible misuse by the authorities there. The evidence available does show that such misuse or abuse occurs frequently, because these hormones are administered in combinations and the farmers have incentives to apply multiple doses.

Q48. To what extent does the scientific evidence referred to by the European Communities assess risks to human health from residues of misplaced implants or improper administration, i.e. when administered differently than indicated on the label of the manufacturer or contrary to GVP, of any of the six hormones? Would your reply have been different at the time of adoption of the EC Directive in September 2003? What are the potential hazards, if any, to human health of the use of large quantities, or doses higher than recommended, of any of the six hormones in dispute?

EC Comments

The criticism of both Dr. Boisseau and Dr. Boobis is based on their understanding that the European Communities did not perform a quantitative risk assessment, which they think is a necessary requirement for a proper risk assessment under the SPS. However, as the European Communities has explained several times in previous questions, this in not required under the *SPS Agreement* as interpreted by the Appellate Body. But as already explained, the European Communities has nevertheless performed a quantitative dose-response assessment in particular with regard to prepubertal children. As the exposure from residues in meat *treated with these hormones according to GVP* was found to lead to residues that exceeded several times the ADIs and MRLs, it is obvious that the higher levels of residues that will inevitably result from misuse or abuse of these hormones will also exceed the ADIs and MRLs recommended by JECFA.

Furthermore, Dr. Boobis states that "…the potential risk, i.e. the probability that effects would occur, would depend on a number of factors...". But as the European Communities has already explained, the risk and risk assessment under the *SPS Agreement*, as interpreted by the Appellate Body, is not the "probability" of the identified risk occurring but the "possibility" of the identified risk occurring under real conditions of use.

Q49. What analytical methods, or other technical means, for residue detection in tissues exist to control the use of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice? What tools are available to control the use by farmers of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice?

EC Comments

To the list of tools listed by Dr. De Brabander to control the possible misuse or abuse of these hormones, the European Communities would add that these hormones should not be sold freely on the counter but by veterinary prescription only. Of course all these apply only for the countries that would be prepared to assume that the possible risk would not undermine their chosen level of health protection.

Q50. Are there other measures available to the European Communities (other than a complete ban) which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

EC Comments

The European Communities notes that the replies by Dr. Boisseau and Dr. De Brabander agree on the point that if GVP is not respected, then the importing country should have the right to restrict imports, even with a total ban, depending on the importing country's chosen level of health protection.

Q51. Does the material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada call into question the potential applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada?

EC Comments

The European Communities understands that the answer by Dr. Boisseau to this question is that the Codex standards would not be applicable. The European Communities also agrees with the statement by Dr. De Brabander.

(g) Other

Q52. Do the risk assessment of the European Communities or any other scientific materials referred to by the European Communities demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes? If yes, why? If not, what kind of evidence would be required to demonstrate such potential adverse affects? Would your response have been different at the time of adoption of the Directive in September 2003?

EC Comments

The European Communities considers that the statements by Dr. Boisseau and Dr. Boobis are scientifically incorrect because they are based on many assumptions and conservative interpretation of the available and constantly growing evidence that directly implicates these hormones in causing and promoting cancer and a number of other adverse effects in humans. If the views of these experts were to be adopted the prerogative of cautious public authorities to regulate risk in order to reduce or eliminate it would completely vanish. Dr. Boisseau and Dr. Boobis apply double standards because they require for the prohibition of these hormones evidence which the pharmaceutical industry did not provide nor did it even examine when it applied for the approval of these substances in the US and Canada in the 1970s and 1980s.

Dr. Boisseau states that: "… the kind of evidence required to demonstrate such potential adverse effects should be (1) toxicological data indicating that the values of the ADIs established by JECFA are not conservative enough, (2) data on residues in treated/non treated cattle and on daily production of hormones in sensitive individuals indicating that the hormonal residue intake associated with the consumption of meat from treated cattle is such that the established ADIs would be exceeded in the case of use of growth promoters." The European Communities submits that such data have been provided and taken into account in the 1999, 2000 and 2002 SCVPH risk assessment, which he has apparently not properly examined.

Dr. Boobis states again that: "… the weight of evidence is that the hormones are not genotoxic in vivo even at doses well above those that would be present in meat from treated cattle (…) However, all of the major reviews in this topic have concluded that whilst there are data gaps, there is no evidence that low level exposure is causing harmful effects in humans (…) However, it should be emphasised that on the basis of the information available, I would rate the risk of adverse effects in humans consuming meat from treated cattle as minimal." (emphasis added). So, according to Dr. Boobis conservative reading of "the weight of available evidence", which means that scientific views outside the mainstream or the majority held view do not count for him, it cannot be excluded that there is a risk, even though this is evaluated by him to be "minimal". However, he does not explain what is "minimal" risk, nor does he seem to pay any attention to the fact that the "gaps in our knowledge – which he admits exist – may indicate that there is scientific uncertainty with potentially disastrous consequences for the consumers.

The European Communities considers that Dr. Guttenplan has rightly summarised the issue: the evidence which the European Communities has presented suggests that "even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen exceeding the daily production rate of oestradiol in prepubertal children". When the evidence is not to their liking, the US and Canada contest the accuracy of the assay originally employed for estrogens at the low levels found in children. However, they consistently refuse, as dose JECFA, to provide their old data in order to examine in an open and transparent manner the kind of assays used by the pharmaceutical industry in the 1970s and 1980s for the approval of these hormones in the US and Canada. But as Dr. Guttenplan rightly points out, recent reports indicate that "more recently reported levels used by the EC are accurate. In addition, levels in post-menopausal women were also very low." Moreover, he explains that: "For pre-pubertal children, even with the low bioavailability of estrogen along with and its low levels in meats, it appears possible that intake levels would be within an order of magnitude of those of the daily production rate. This is greater than FDA's ADI and suggests some risk to this population."

Q53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations? Would the systematic use of these and the synthetic hormones in combination have any implications on how the scientific experiments and the risk assessments are to be carried out? If so, have the scientific materials referred to by the European Communities or relevant JECFA reports taken into account the possible synergistic effects of such combinations on human health? [see sections 4.2-4.3 of the Opinion of the SCVPH of 2002 in US Exhibit 1]

EC Comments

The European Communities notes that both Dr. Boisseau and Dr. Guttenplan recognise that the statement by the European Communities is correct. Dr. Boisseau's reply is, however, partly false because it ignores the potential stimulatory estrogen receptor mediated effects of estradiol on cell proliferation which tend to be increased by progestins (see *New Eng. J. Med., 354, 270-282, 2006).*

Moreover, Dr. Guttenplan accepts that "… in principle the use of mixtures should complicate risk assessments/scientific experiments, as they would have to evaluate/investigate each component alone and in combination. This is a major undertaking as effects of individual agents may be additive, inhibitory, and synergistic or there may no effect." What is even more important, he acknowledges that "… it appears that no experiments on effects of combinations were performed, so some uncertainty exists there." The European Communities submits that this is still another kind of uncertainty that should be taken into account by the Panel in deciding whether the evaluations by JECFA are credible and reliable.

Q54. What is the acceptable level of risk reflected in the Codex standards for the five hormones at issue? How does this compare to the European Communities' stated objective of "no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion". [see para. 149 of EC Rebuttal Submission (US case)]

EC Comments

The European Communities notes that Dr. Boisseau and Dr. Boobis differ as to the acceptable level of risk reflected in the Codex standards for the five hormones at issue: the first argues that Codex's "... ADI represents the quantity of these residues which can be ingested daily by consumers over life time *without causing any problem* of health ...", but the reply of the second suggests that the level is "*no appreciable risk with daily exposure*". If one were to follow Dr. Boisseau's reply, then there is no doubt, and most of the experts have explicitly accepted it, that there is a risk although for some of them – like Dr. Boobis - this is viewed as "minimal". On the other hand, if Dr. Boobis' reply is followed, this would mean that Codex's standard recognises that there is an scientifically identified risk but recommends its members to follow it because it thinks (as a risk manager) that it is "not appreciable". If that were the case, however, Codex and the *SPS Agreement* cannot oblige a sovereign country to accept a risk, whether it is viewed as small, medium or big. This is the autonomous right of each member to decide and the Appellate Body has explicitly said that WTO members have the right to fix a level of protection of "zero risk".

For the benefit of Dr. Guttenplan, Codex has not set an ADI or an MRL for MGA yet, since no decision has been taken by the Codex Alimentarius Commission. So, no international standard exists for MGA yet.

Q55. Do the Opinions of the European Communities or other scientific materials referred to by the European Communities evaluate the extent to which residues of growth promoting hormones in meat contribute to what the European Communities calls "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings"? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 151 of EC Replies to Panel Questions, paras. 43-44 of US Rebuttal Submission, paras. 83-85 of Canada's Rebuttal Submission]

EC Comments

The European Communities disagrees with Dr. Boisseau's reply that its position is "a position of principle" or that it is based on economic grounds (as he implied with his reply to the previous question). The time, effort and money spent by the European Communities to clarify the scientific issues identified by the Appellate Body in its 1998 report on *Hormones* clearly establish that the EC's position and legislation are based on sound and up to date scientific grounds. The precautionary principle comes after proper consideration of the scientifically identified and analysed risk.

Dr. Boobis accepts that additive risks arising from the cumulative exposures is a scientifically sound approach and that can and is done in some cases. From his reply, one may infer that he accepts that this is not done by JECFA nor by the US and Canada. He only thinks this is not appropriate for these hormones because of his preconceived approach that there is a dose-response relationship (threshold) in the carcinogenic mode of action of these hormones.

The European Communities disagrees with the statements by Dr. Boisseau and Dr. Boobis for the reasons that have been developed extensively in its submissions and in some of its comments above. It urges the Panel to disregard their comments because they are purely theoretical and for the additional reason that they come from two experts that have never done any specific research on these hormones

nor have they ever published something on these substances. Instead of criticising the risk assessment produced by the European Communities, these experts should have examined in their replies whether such an additive risk assessment ought to have been examined by JECFA in the first place before issuing the recommendation that the risk is "not significant".

The European Communities notes that Dr. Guttenplan would have liked to see much more evidence in the 1999 SCVPH assessment. To the extent this was not provided in 1999 and in 2002, this is not because of omission but because the state of scientific knowledge available by then – i.e. the gaps and scientific uncertainty clearly identified in those opinions – did not allow such an assessment to be completed.

Q56. Has JECFA/Codex considered in its risk assessment of the five hormones such "additive risks? Are there internationally recognized guidelines for conducting assessments of "additive risks"?

EC Comments

The European Communities disagrees with both Dr. Boisseau's and Dr. Boobis' replies. They provide no precise reference of where in the JECFA 2000 report it is stated that such a cumulative risk assessment was carried out. The European Communities understands that such a cumulative assessment of the additive risk has not been performed (and this is also what apparently Dr. Guttenplan believes, as words seem to be missing from his reply).

The European Communities notes that it has clearly been shown that the effects from exposure to different estrogens are additive; i.e. when several estrogens are given simultaneously at concentrations where none of them alone results in any detectable effects, the combined exposure leads to a clear effect. Thus, any additional dose will lead to an increased effect (Rajapakse N., Silva E., Kortenkamp A.: Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action., Envir. Health Perspec. 110, 917-921 (2002); and Tinwell H., Ashby J.: Sensitivity of the Immature Rat Uterotrophic Assay to Mixtures of Estrogens, Envir. Health Perspec.112, 575-582 (2004)). Moreover, there are several hormonal preparations containing two hormones (estradiol plus trenbolone) and there are several publications in the animal science literature recommending different preparations in consecutive applications. Therefore, the additive risk needs to be carefully evaluated. For instance, trenbolone as such has a complex hormonal activity (at the same time progestin, androgen and glucocorticoid). Estradiol and trenbolone residues therefore may have 4 different hormonal activities.

The European Communities further notes that although there is agreement that "there is no international agreement on how to undertake a combined risk assessment of compounds acting by the carcinogenic mechanisms suggested by the EC for the hormones, i.e. genotoxicity via direct or indirect interaction with DNA", yet the performance of such a risk assessment is not impossible. The European Communities has tried to do such an assessment when the information available was sufficient, but could not complete it because of gaps in our scientific knowledge.

Q57. Canada comments that "one single molecule that the European Communities considers so dangerous from meat derived from animals treated with hormone growth promoters is suddenly not at all that dangerous when consumed from meat from animals treated for therapeutic or zootechnical purposes. The European Communities' concern about the genotoxic potential of oestradiol-17β suddenly and inexplicably disappears." To what extent are hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes, taken into account by the European Communities, if at all, in its assessment of the cumulative effects from the consumption of meat containing residues of the hormones at issue? Would your reply have been different at the time of adoption of the EC

Directive in September 2003? If so, why? [see para. 97 of Canada Rebuttal Submission; paras. 17-20 of US Opening Statement]

EC Comments

The European Communities considers that asking this question in the first place was unnecessary and irrelevant, because the Appellate Body did not find any violation from the use of some of these hormones for therapeutical or zootechnical purposes. As Dr. Guttenplan points out, the conditions imposed by the European Communities for such limited use are such that it would not be possible to undermine its chosen level of protection.

Therefore, the European Communities is consistent because the use of oestradiol for such purposes is now virtually terminated.

Q58. Please comment on the EC statement in para. 94 of the EC Replies to Panel Questions that "the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be", taking into account para. 105 of Canada Rebuttal Submission.

EC Comments

The European Communities needs to clarify that the quoted statement was made in response to the US and indeed Canadian argument that there is no risk from cumulative exposure to residue of these hormones in meat treated with one or several of these hormones for growth promotion purposes. Moreover, the statement is framed cautiously to say "is likely to be" precisely because such a complete cumulative risk assessment has not been carried out by JECFA and the other countries. Moreover, if the assumption of JECFA and of the US and Canada that there is a threshold is false, the relevance of the EC comment is a realistic eventuality. The European Communities has in fact provided the Panel with recent evidence (e.g. the papers by Dr. D. Sheehan, see Exhibit EC-87) which has showed the absence of such a threshold. It is indicative that none of the experts discuss it in his replies. The studies mentioned in these exhibits show that under the circumstance that the endogenous hormone is active, there can be no threshold unless metabolism is 100% effective before the dose reaches the target tissue. It is also noteworthy that none of the scientists discusses the reference made by the European Communities to the US 2002 Carcinogenesis Report which states as regards oestradiol that residues in meat from animals treated with hormones for growth promotion lead to levels higher than the endogenously produced ones. The question therefore is by how much and of what kind of biological and toxicological nature. In the EC's comments to previous questions, it has been shown that the level of residue formation in meat can be significantly higher and may contain residues from different metabolites. It seems therefore that the experts criticise the European Communities for making an assumption, but they are not apparently able to prove either that their own assumption is correct.

Q59. Does the scientific evidence referred to by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see para. 132 of Canada Rebuttal Submission]

EC Comments

The European Communities notes the different views which the replies of the scientists display on this critical question. Dr. Boisseau accepts that such adverse effects have been identified, but faults the European Communities for not having conducted a "quantitative" risk assessment. Dr. Boobis

continues with his line of argument that there is a threshold effect, which prevents this kind of adverse effects on the immune system from occurring. The point, however, is that neither the US nor Canada (and a fortiori nor JECFA) have identified such adverse effects because of the outdated nature of the data on which they based their assessments. The European Communities has offered some serious evidence, some of which appeared for the first time recently, and pointed to a number of gaps and uncertainty in our knowledge. This is recognised by Dr. Guttenplan, who states that "…there is evidence that estrogens can be involved in Lupus, rheumatoid arthritis, thyroiditis. In addition the development of allergies is thought to be at least partially related to estrogens. The studies in experimental animals also did not identify any immune-related effects, although it is not certain the types of possible effects in humans would be detected in experimental animals…". The question, therefore, is the degree of confidence by which the US and Canada (and JECFA) can ensure the Panel that such adverse immune effects are not possible to occur from residues in meat treated with these hormones for animal growth promotion. The European Communities thinks they have failed to do so to the required standard of proof.

Q60. Does the scientific evidence referred to by the European Communities identify and evaluate whether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives (MGA) or implanted? Are you aware of any differences?

EC Comments

The EC contests the accuracy of the statements by Dr. Boisseau and Dr. Boobis. It is known that MGA is the only hormone that is administered as a feed additive, which confirms that the bioavailability of this hormone is rather high. Moreover, it has been shown that MGA is highly lipophilic and accumulates in adipose tissue. The 1999 and 2002 SCVPH and exhibits EC-14, 16 and 19 have shown that the route of administration of MGA is conducive to misuse or abuse, as the residues of MGA detected in the US samples of meet were much higher than the levels which should have been normally expected (exhibit EC-16). The study mentioned in exhibit EC-16 has also shown that the residues in fat of oestradiol-17β increased by about 300% following labelled MGA treatment. The consequence of this is that given the tremendous "boosting" effect which MGA has on the residues of oestradiol in meat and the easiness by which its administration can be misused, the possibility to increase substantially the level of residues, and hence the risk of cancer, is significantly increased. This is not examined either by Dr. Boisseau or Dr. Boobis, who apparently have not read this material.

Hormone MGA has been in use in the US and Canada since the 1970s and it is interesting to note that JECFA has not been seized of a request to evaluate it until 2000. Yet, until today there is no Codex standard for MGA. It is also clear that the evidence upon which JECFA based its evaluation has not been made available to anyone, has not been published in peer-reviewed journals and it is outdated but today's standards. The most important evidence on MGA is the one generated by the EC following the Appellate Body 1998 hormones decision. This information is publicly available and demonstrates the gaps in our knowledge, the uncertainty surrounding this hormone and the multiple risks which the administration of MGA poses to human health.

As regards the risks from eating meat treated with implanted hormones, the evidence shows that non-removed implants contain milligrams of residues. These are 10^7 to 10^9 fold more residues than present in the peripheral tissue (pikograms per gram). The total dosage in an implantation site is therefore about a thousand fold higher than the residues in the whole carcass of the animal. There is no doubt that the risk from implanted hormones is in a completely different order of magnitude from the risk posed from untreated animals. Dr. Boobis makes again his unfounded statement that: "However, whilst this would lead to increased exposures, it is still unlikely this would exceed the ADI, and

certainly not for any period of time. It is also an unlikely occurrence in view of the way in which the hormones are used and controlled." First of all, he has and provides no factual basis to argue that it is "unlikely" that misuse will exceed the ADI. Neither Codex nor JECFA have fixed yet an ADI, and even if they were to do it one day, he has now no data to suggest that it is unlikely to be exceeded. Moreover, it has already been shown that even the administration of MGA that does respects GVP leads to a tremendous "boosting" effect on the residues of oestradiol in fat and the attending risk of exceeding the ADIs is very high.

Q61. In your view and in the light of information provided by the parties as well as the work undertaken at JECFA and Codex, did the scientific evidence available to the European Communities at the time it adopted its Directive (September 2003) allow it to conduct an assessment (quantitatively or qualitatively) of the potential for adverse effects on human health arising from the consumption of meat from cattle treated with (a) progesterone; (b) testosterone; (c) trenbolone; (d) zeranol; and (e) melengestrol acetate? Would your response differ in light of the scientific evidence provided which is subsequent to the adoption of the EC Directive?

EC Comments

The reply of Dr. Boisseau is surprising as the data available to the EC are mentioned in the 1999, 2000 and 2002 SCVPH assessments and the additional evidence from other sources is explained in the written submissions of the EC to the Panel and were provided as exhibits thereto. It is recalled that he has explicitly admitted that he has not done nor published any work on these hormones.

The reply by Dr. Boobis and Dr. Boisseau can only be explained by their exclusive reliance on the JECFA reports, which Dr. Boobis thinks represent the "weight of the evidence" that should be taken into account. This is probably not surprising, as they have both served in the JECFA panel that examined some of these hormones, although they both lack any specific expertise on these hormones, as they have not carried themselves any experiment on them when used for animal growth promotion purposes.

Their entire reasoning – whose objectivity and impartiality is therefore in great doubt for the reasons the EC has explained to the Panel during the expert selection procedure - is based on the assumption that there is a dose-response relationship (threshold), despite the accumulation of so much recent evidence showing that this assumption can no longer be valid for a number of these hormones, certainly for oestradiol 17β, progesterone, testosterone and zeranol. Their reasoning is also based on the idea that a risk assessment to be acceptable has to perform a quantitative analysis and assessment of risk even of aspects for which the available evidence is insufficient or there are total areas of gaps in our knowledge.

The EC considers that the reply by Dr. Guttenplan, as well as those by Dr. Shippel, Dr. De Brabander and Dr. Cogliano who have not expressed themselves on this precise question but this can be seen from their replies to the other questions, show that there is sufficient evidence which "does indicate that potential adverse effects exist for all of the hormones. However, the ability to make a risk assessment (qualitative or qualitative) does vary between compounds." (Dr. Guttenplan). The available evidence, at the varying degrees mentioned by Dr. Guttenplan, does establish that "… accurate ADI's cannot be established at this point", and that "… studies in experimental animals and studies on levels in beef are still needed." Most importantly, the EC agrees that "from the data available at the time of the Directive, the potential for adverse effects could not be ruled out."

Q62. Does the scientific evidence relied upon by the European Communities support the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge

now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why?

EC Comments

The EC considers that its comments on the positions of Dr. Boisseau and Dr. Boobis to the previous question no. 61 are equally and fully applicable here.

It is difficult to grasp the idea of Dr. Boisseau for a temporary risk assessment, unless his statement was to be understood that the gaps and uncertainties identified by the EC in its risk assessment are such as to require further research and investigation.

As regards the long and dismissive reply by Dr. Boobis, who despite his lack of any specific expertise on these hormones tried to discredit all the studies mentioned by the EC, it is now clear on the basis of a more careful examination by a real expert of the same body of evidence that it would necessarily lead to the opposite conclusion. Dr. Boobis' comments on the studies generated by the EC are flawed in almost all respects.

For instance, he comments on the Leffers et al., 2001 study on the low-dose effects of Zeranol and other estrogens on gene expression in MCF7 cells. He writes: "Many of the changes will reflect the proliferative response to an oestrogenic stimulus". However, in the applied assay changes in gene expression were assayed after 24h exposure, whereas the first up-regulation of proliferation-sensitive genes becomes detectable after 36h exposure. Thus, the observed effects are a likely direct consequence of gene activation by the estrogen receptor, reflecting activation of the receptor by Zeranol and the other compounds. (see Jorgensen M., Hummel R., Bevort M., Andersson A.M., Skakkebaek N.E., Leffers H.: Detection of oestrogenic chemicals by assaying the expression level of oestrogen regulated genes. APMIS. 1998 106:245-51.)

Another example is that he dismisses the bovine metabolism of oestradiol-17β and oestrogenic potency of fatty acid residues on the unsubstantiated ground that "the difference in potency from the parent hormone is not very great or even apparent at low doses, where effects were minimal", where the opposite is rather true in the study cited. Another example is that he dismisses the relevance of the studies on misuse and abuse on the speculative ground that "… the probability that this would occur is extremely low". However, he has no evidence and provides no credible basis for that conclusion. Still another example is that he dismisses the relevance of the recent findings on the mutagenicity and genotoxicity of oestradiol-17β despite the fact that this has been shown both in vitro and now in vivo. The findings of the study he criticises for no valid reason have been largely confirmed in other recent studies supporting a role for the estrogen metabolites which include the genotoxic, mutagenic estrogen quinones in estrogen carcinogenicity (New Eng. J. Med., 354, 270-282, 2006). And the list of examples showing lack of specific knowledge or impartial presentation of the available evidence by Dr. Boobis is much longer.

Conversely, a more considered and objective view is to be found in the reply of Dr. Guttenplan, who provides some examples of the areas in which gaps and uncertainties have been identified and indicates some of the additional research that is required before the EC would be able to conduct a more complete risk assessment. The EC agrees with his comments.

ANNEX F-2

COMMENTS BY THE EUROPEAN COMMUNITIES ON THE REPLIES OF CODEX, JEFCA AND IARC ON QUESTIONS POSED BY THE PANEL

(30 June 2006)

Introduction

The European Communities appreciates this opportunity to comment on the replies of the international bodies to the questions posed to them by the Panel. The European Communities considers it necessary to recall the position it has already expressed to the Panel at the time it decided to ask questions from these bodies, namely that Codex and JECFA lack appropriate and transparent procedures for submitting this kind of comments and replies to other international organisations, such as the WTO dispute settlement bodies. In particular, replies and comments that come simply from the secretariat of those bodies, without following the legally required procedures for their internal elaboration and transmission, should be disregarded because they are likely to influence unlawfully the Panel's deliberations.

The European Communities notes that the comments submitted in these cases by those bodies do not explain whether the required internal rules and procedures for their adoption have been fully respected. Therefore, the European Communities requests the Panel to clarify this question with these bodies; in the absence of an adequate and legally sound reply – with precise references to the rules that were applied in the elaboration of their replies - the European Communities would request the Panel to disregard them.

Q1. Please briefly describe the procedure for the elaboration and adoption of an international standard by Codex. What is the decision-making process for the adoption of an international standard?

EC Comments

The European Communities notes that according to Codex: "In the case of MRLs for veterinary drugs, submission of project documents is not required; instead, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) prepares a priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA, which is submitted to the Commission for approval." However, it is noteworthy that this procedure was not followed when JECFA decided to re-evaluate the three natural hormones in 1999, because the CCRVDF did not request such a re-evaluation.

The European Communities also notes the statement whereby: "The Commission attaches a great importance of achieving consensus at all stages of the elaboration of standards and that draft standards should, as a matter of principle, be submitted to the Commission for adoption only where consensus has been achieved at the technical level." However, the European Communities draws the attention of the Panel to the uncontested fact that the 1988 Codex standards for the five hormones (except MGA) were not adopted by consensus and the 1999 review by JECFA of only the three natural hormones were not even presented to Codex for adoption because the relevant committee [CCRVDF] decided not to consider them as it had not requested their re-evaluation.

Q2. Please briefly explain the differences between Codex standards, codes of practice, guidelines, principles and other recommendations.

EC Comments

The EC has no comments at this stage.

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

EC Comments

As the European Communities explained by its comments to question no 3 of the Panel experts questions, its legislation complies with the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius,* which where adopted by Codex in 2003, and these working principles were complied with in the assessment of the six hormones at issue and in the adoption of the Hormones Directive 2003/74/EC.

The European Communities further notes the statement that: "Following the adoption of the Working Principles, the Commission requested that relevant Codex Committees develop or complete specific guidelines on risk analysis in their respective areas for inclusion in the Procedural Manual…The two documents will be considered by the 30th Session of the Codex Alimentarius Commission in 2007 (after review by the Codex Committee on General Principles) for adoption and inclusion in the Procedural Manual." This statement confirms the EC position (see also its comments to question no 3 of the Panel experts questions) that until now there exist no guidelines on risk analysis for residues of veterinary drugs in the sense of Article 5.1 of the *SPS Agreement*. The consideration in 2007 of the two working documents does not mean that they will be adopted, if one were to judge from previous experience in the work of the Codex Committee on General Principles.

The European Communities also draws the attention of the Panel to the statement that the principles to be adopted one day will "…define the responsibilities of the various parties involved: the responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods, while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA)." This confirms again the EC position (see also the EC comments to question no 5 of the Panel experts questions) that such a clear definition of the responsibilities does currently not exist, and that in reality it is JECFA that is informally doing also the risk management, leaving practically no real risk management choice to the Codex members to adopt measures aiming to achieve a high level of health protection. This is clearly the situation in the case of the six hormones in dispute, since the old data used by JECFA and the way in which it drafted its reports (e.g. "genotoxic potential", "unlikely to be exceeded", "pose an insignificant risk", "MRLs considered unnecessary", etc.) in effect deprive the Codex members from applying a very high level of protection, which in the context of the WTO can be "no or zero (additive) risk" according to the Appellate Body.

The European Communities considers that the reply of JECFA confirms the EC position that there exists currently no international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues in food. What JECFA calls "key international risk assessment documents" are in reality nothing more than informal papers prepared for certain specific purposes and substances which were never presented for consideration and adoption by the competent decision-making bodies of Codex Alimentarius Commission and JECFA. They do not have, therefore the status of legally binding risk assessment techniques in the sense of Article 5.1 of the *SPS Agreement*. In fact, if such risk assessment techniques already existed, quod non, there would have been no need to start this kind of work in the CCRVDF in 2000. Indeed, the reply of Codex to the next question (No 4) confirms explicitly the accuracy of the EC position.

It should be further clarified that the above EC comments do not intent to diminish the work that is being done in the framework of Codex and JECFA, which is of importance primarily for the countries which do not have in their internal legislation such rules and procedures on risk assessment. The informal technical work to which JECFA and Codex refer cannot, However, be invoked to resolve differences between the parties in a formal WTO dispute settlement with very serious legal, health and economic consequences for the parties to the dispute. This could be the case only when Codex and JECFA formally adopt some time in the future the relevant standards on risk assessment for this kind of residues of veterinary drugs in food. As the European Communities has explained with its comments on question no 3 of the Panel experts questions, its internal legislation on risk assessment applied to the six hormones in question is far more advanced than the informal working documents to which Codex and JECFA referred to in their replies.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

EC Comments

The European Communities notes the reply of Codex that: "There is no adopted Codex standard or related text on the risk assessment of residues on veterinary drugs that provides guidance to governments (…) the CCRVDF in 2000 started develop texts on risk analysis principles (…) The documents may be adopted by the Commission in 2007". This statement confirms clearly the EC position that such standards or guidance are absent in the relevant legal framework. The European Communities also notes the Codex reply "[no] standard *or related text*", which clarifies that there is absence not only of standards but also of guidelines and recommendations, in the sense of Articles 3 and 5 of the *SPS Agreement*.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) as defined by Codex and explain how they differ.

EC Comments

The European Communities has no specific comments other than to recall that its legislation, as applied to the six hormones, complies fully with the three components and actually goes further than the Codex work in progress. It is, however, true that there are some differences between the European Communities' and the US' and Canadian conception of these steps, as Drs. Cogliano and Guttenplan have explained in their replies, and the question is which philosophy will eventually prevail in the future work of Codex. The basic differences between the European Communities and the US and Canada reside, *inter alia*, in that the European Communities (i) is more strict with potentially genotoxic substances, (ii) does not always require a quantitative assessment of the risk (a qualitative assessment is acceptable when the data support it), (iii) pays more attention to scientific uncertainty and (iv) applies a higher level of health and environmental protection.

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

EC Comments

The European Communities has no specific comment at this stage other than to refer the Panel to its comments on question no 3 of the Panel experts questions.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? [see Canada's comments in para. 72 of its Rebuttal Submission]

EC Comments

The European Communities notes the reply of JECFA whereby "(…) most risk assessments of chemicals today on a national and international level are deterministic, i.e. they use a point estimate for the toxicological endpoint and a point estimate for the exposure assessment (…) this is (…) often a necessity due to the information at hand. Uncertainties around these point estimates should be considered in the risk assessment process. The current risk assessment process, which includes consideration of sensitive subpopulations, is considered to be sufficiently conservative to be public health protective." The European Communities also notes the reply whereby "(…) increasing efforts are under way (…) to explore methods to perform probabilistic risk assessment, i.e. include distributions rather than point estimates in the risk assessment process (...) however probabilistic methods in the toxicological assessment are not yet internationally agreed and are not yet commonly applied (…) the outcome of a probabilistic risk assessment is much more difficult to interpret and apply by risk managers." More important is JECFA's comment that: "(…) the probabilistic or deterministic approaches can be applied, independent if a compound is assumed to act via a threshold mechanism, i.e. non-linear, or not. JECFA's assessment process is based on the mechanism of action of the compound to be evaluated, non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect. In such a case, as for the hormones, a no-effect-level can be determined from which an ADI can be established."

These comments confirm the EC point that JECFA assumes non-linearity, but dos not look for it nor does it attempt to prove it. If JECFA's guess about the mechanism of action of the hormones is wrong, as the evidence submitted by the European Communities shows, then its assumption of non-linearity (on safe threshold) is obviously wrong. It is recalled again that in the 1999 assessment, JECFA concluded that oestradiol 17 β has "*genotoxic potential*", it found that progesterone "*on balance*" is not genotoxic, and that the evidence on testosterone was ambivalent. This shows that a slight error when JECFA draws its balance of the evidence can be catastrophic for human health, as its was with so many substances in the past, and most clearly with the evaluation of Carbadox referred to by the EC in its rebuttal submissions (at paras. 150-152 of US panel).

The Panel would have to understand that these comments by the European Communities are not trivial. Dr. Boobis (like JECFA) came to the conclusion that these hormones are not genotoxic on the basis of the so-called "weight of the evidence" approach, meaning that in their view the majority of the evidence does not yet accept that they are genotoxic by a direct mechanism of action, and this is because on their view there are not yet enough experiments *in vivo*. This, however, is disputed by the European Communities on the basis of evidence conducted both *in vitro* and *in vivo*.

Finally, JECFA states that in its reports and in the toxicological monographs on the safety assessment of the hormones it has"(…) used risk assessment principles particularly targeted to the evaluation of such substances (…) [and has considered] (…) other relevant toxicological end-points, such as reproductive toxicity, genotoxicity and potential carcinogenicity." The European Communities

contests the scientific accuracy and truth of this statement, because JECFA did not consider carefully many important end-points, such as the effects on pre-pubertal children, on the immune system, endocrinological effects, etc. The European Communities refers the Panel to the replies of Drs. Cogliano, Sippel and Guttenplan to the Panel questions in this regard.

Q8. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

EC Comments

The European Communities first likes to clarify that the question should have not asked whether there are "JECFA or Codex materials" but "JECFA or Codex materials that have been lawfully approved by the members of the Codex Alimentarius Commission". Furthermore, the European Communities considers that there is no reason to evaluate differently chemicals as opposed to biological or physical agents. The dose-response assessment can be done both qualitatively and quantitatively, if the data so permit. The European Communities has done a qualitative assessment in the case of these hormones. The difference is that JECFA based its findings on a no-effect-level only, whereas the European Communities found also that there is no safe threshold.

Q9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

EC Comments

The European Communities notes that the above definition from the 66 JECFA meeting, which covers also metabolites and associated impurities, was not the one followed when JECFA evaluated these hormones. Moreover, the definition of an ADI does not mean that there is no risk, as the defending parties and JECFA imply, but that there would be no "appreciable health risk". But whether the risk is "appreciable" or not is for each WTO Member to decide. This is precisely the function of its desired level of health protect which can be no (or zero) additive risk, and which is the level of protection applied by the European Communities in the case of these hormones when administered for animal growth promotion purposes.

Q10. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please also identify and describe any steps that are taken in the risk assessment process to build a margin of safety into to the final recommendation.

EC Comments

The European Communities notes that according to JECFA, "(…) in setting ADIs, an attempt is made to take account of special subpopulations that may be exposed." However, as the European Communities has shown, this is not properly done in the case of these hormones because the data used by JECFA for the endogenous production by pre-pubertal children are no longer valid. Moreover, JECFA states that it "(…) uses the risk assessment process when setting the ADI, i.e. the level of "no apparent risk" is set on the basis of quantitative extrapolation from animal data to human beings." This statement contrasts with its statement to the previous question, where it claims that it performed a qualitative assessment. In any case, whether qualitative or quantitative, JECFA did not use in all of

its calculations data from residues in meat from animals treated with these hormones for growth promotion purposes, as it is erroneously stated by the defending parties and the Codex and JECFA.

The European Communities also notes that JECFA "may recommend MRLs "not specified" or "unnecessary" when there is a wide margin of safety of residues when compared with the ADI (...)" and that "(…) JECFA may determine that MRLs cannot be recommended because of significant deficiencies in either residue data or available analytical methods or when an ADI is not established." It is crucial to note, however, that in the case of the three natural hormones JECFA did not specify MRLs because it found them "unnecessary". But this is utterly unscientific because there is no "wide margin of safety" for residues of these hormones given that it has been already established clearly that the endogenous circulating levels alone have been found to cause cancer for some individuals. It was, therefore, imperative for JECFA to evaluate the additive risk that the residues in meat from treated animals can pose to human health. This JECFA has failed entirely to do so, for the simple reason that there are currently no sufficiently powerful analytical methods to detect the origin of residues from the three natural hormones in meat, i.e. whether they are of endogenous or exogenous source. This is the only true reason for which JECFA did not specify MRLs in 1988 and in 1999, after it had found that an ADI had to be established. This is clearly stated in the 1988 evaluation of the three natural hormones by JECFA, where it is explicitly stated:

> "The Committee concluded that residues arising from the use of oestradiol-17β [and progesterone and testosterone] as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health. The Committee recognized that most methods of analysis for orstradiol-17β [and progesterone and testosterone] are radioimmunoassays, which usually have a large co-efficient of variation at the concentrations being measured. While these methods may be satisfactory for measuring oestradiol-17β [and progesterone and testosterone] levels in experimental situations, improvements would be needed if routine analytical methods for the control of residues were required. On the basis of its safety assessment of residues of oestradiol-17β [and progesterone and testosterone], and in view of the difficulty of determining the levels of residues attributable to the use of these hormones as growth promoters in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level [i.e. an MRL]" (see WHO Technical Report Series no 763, page 19, 1988).

However, this passage from the 1988 JECFA report on the three natural hormones has now mysteriously disappeared from the 1999 JECFA report on these hormones without any explanation, other than that there is now "a wide margin of safety". So, JECFA finds itself now in the paradoxical situation of having for the first time to establish ADIs for the three natural hormones but is not in a position to fix MRLs for their residues! And the explanation it has offered was to say that they are "unnecessary". But are they really "unnecessary", given the endogenous production levels by prepubertal children and the widespread misuse and abuse of these hormones found in the US and Canada?

The European Communities would suggest to the Panel to ask JECFA to clarify its position on these precise points.

Finally, it is also interesting to note that according to JECFA "[A]s a general principle, the Committee will not normally recommend an MRL that results in residue levels that lead to dietary intake exceeding the ADI based on toxicological or microbiological considerations." The European Communities has demonstrated that there is such a clear possibility of the ADIs being exceeded routinely. As the European Communities has explained in its Written Submissions, this has been explicitly recognised also in the US Carcinogenesis Report since 2002, and it is confirmed by the

replies of the experts to the questions of the Panel, in particular those of Dr. De Brabander and Dr. Sippel.

Q11. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

EC Comments

The European Communities notes that there is a wide discrepancy between the theory and reality, in particular given the narrow mandate of JECFA, the potentially subjective interpretation of the data, and the opaqueness of its procedures and the data it uses in its assessments. JECFA's reply does not convince because it does not provide the data upon which it based its assessment for verification and peer-review by independent scientists.

Q12. In paras. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

EC Comments

The European Communities notes that the replies of both Codex and JECFA confirm that the latter does not have the mandate to examine risk management options other than to propose or not ADIs and MRLs, and it has not been asked to consider such options when it examined these hormones. Moreover, both Codex and JECFA appear to have an extremely narrow understanding of what constitutes risk management: for instance, they appear to think that the question whether an identified (and characterised) risk is or is not "appreciable" is a risk assessment issue. This is not correct, as this issue is by definition a risk management question and it is a function of the chosen level of protection by the risk manager. A risk assessor's role, like that of JECFA, should be to identify only if there is a risk and to explain any scientific uncertainties that may surround its assessment. Its assessment of the risk may be qualitative or quantitative, but the decision whether a scientifically assessed risk (e.g. of cancer) is "significant" or "appreciable" is, strictly speaking, a risk management decision. It follows that JECFA does perform also risk management functions in the Codex system, despite its formal denial of doing so.

Q13. With respect to the data used in the evaluation of chemical substances, such as the hormones at issue, what are the data requirements for JECFA's work and how are they determined? Who provides data for such evaluations? Are any records/archives kept by JECFA? Do any confidentiality rules apply to data submitted to JECFA or should all data be publicly available? If confidentiality rules apply, in which circumstances? [see paras. 95-96 of EC Rebuttal Submission (US case), paras. 78-79 of EC Rebuttal Submission (Canada case), para. 123 of Canada Rebuttal Submission]

EC Comments

The European Communities would note the following statements by JECFA:

- "the data are mainly provided by companies who produce the compounds;

- the submitted data may be published or unpublished and should contain detailed reports of laboratory studies, including individual animal data;
- summaries in the form of monographs are helpful, but they are not in themselves sufficient for evaluation;
- the unpublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA;
- neither FAO nor WHO have facilities for storing printed data for long periods of time, so confidential data will either be returned to the submitter at the submitter's expense or destroyed after the evaluations have been completed;
- key material can be stored up to five years and will then be destroyed."

These statements confirm the EC position that JECFA has had access to the detailed reports provided by the industry, but failed to provide them to the European Communities. The European Communities has been asking for these confidential and unpublished data since 1999, so JECFA cannot pretend that it had destroyed them already at that time!

JECFA claims that "it is important to note that JECFA evaluations are completely publicly available, and a detailed description of the data evaluated is accessible through the monographs." But these monographs are not the original of the data used but processed and reworked information which does not enable scientists to verify the accuracy of the design of the study, of the experiments carried out, of the interpretations made and the conclusions drawn and for what reasons. The European Communities has not been asking for information regarding "the manufacturing process of substances, which are considered confidential for commercial purposes", but for the specific scientific studies (toxicological and residues analysis) in order to verify the scientific validity of these studies and the accuracy of the conclusions drawn by JECFA (and the defending parties). The European Communities has rendered public and provided its own studies to all the parties; therefore, it fails to understand why the US, Canada and JECFA (and Codex) continue to deny access to their own data.

The European Communities reiterates, therefore, its standing request to the Panel to order the production of their so-called confidential and unpublished data, if the credibility of their assessments and of this process is to be maintained. Otherwise it has to draw the necessary negative inferences from the failure to provide the requested data.

Q14. How are experts involved in JECFA's work selected? What are the selection criteria?

EC Comments

The European Communities simply notes that in the evaluation of the six hormones by JECFA have participated scientists who have no specific expertise on these hormones, like Drs. Boisseau and Boobis, since they have not worked on nor have published anything on these substances when used for animal growth promotion purposes. From the JECFA reply it is not clear to the European Communities whether the selection of JECFA's experts is as strict as that applied in the case of IARC (see its reply to Panel question no 22). The European Communities would ask the Panel to clarify further this point.

Q15. Please provide the definition of the term Good Veterinary Practice (GVP). Are there any relevant Codex standards, guidelines, or recommendations relating to GVP?

EC Comments

The European Communities notes that there is currently no definition nor guidelines on GVP in Codex and JECFA, as this is confirmed by the replies of Dr. Boisseau and Dr. De Brabander (question no 44 to experts).

Q16. Please provide an update on the status of international standards with respect to the six hormones at issue. What are the remaining procedures before the adoption of a standard on melengestrol acetate (MGA)? What is the timeframe for their completion?

EC Comments

The European Communities notes that the Codex standards on the five hormones were adopted by a very slim majority vote in Codex, despite the Codex' statement that decisions are taken by consensus. Indeed, the Codex standards were adopted in 1995 with 33 votes in favour, 29 votes against and 7 abstentions, that is by a minority of the members present and voting (see para. 4.77 of the 1997 Panel report, WT/DS26/R/USA, at page 39). Their assessment by JECFA dates of 1988. The Codex reply also confirms the EC position that currently there exists no standard for MGA.

Q17. Is the table in Exhibit CDA-32 outlining the chronology of JECFA's assessment of the hormones at issue and the resulting documentation complete?

EC Comments

The European Communities wishes to clarify that the 66th JECFA meeting (held 20 - 28 February 2006) deliberated on the MRLs previously proposed for melengestrol acetate. It did, however not consider any new data but limited itself to the correction of a calculation error. The EC highlighted this during the recent 16th Session of the CCRVDF that no original data were presented in the review (see ALINORM 06/29/31 paragraph 69).

Q18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

EC Comments

The European Communities notes the statement that "in the case of estradiol-17 beta, progesterone and testosterone, they were re-evaluated by the 52n JECFA (1999) at the initiative of the JECFA Secretariat", and that "the 12th CCRVDF (2000), in recognising that it had not requested the re-evaluation of the three substances and that the new MRLs recommended by the 52n JECFA did not differ significantly from the current MRLs, decided to not consider the new recommendation of the 52nd JECFA." There are many comments one can make on this statement. First, it is quite unusual for substances to be re-evaluated at the request of JECFA's Secretariat, despite the written request of one of its members (who represented at the time 15 countries) to postpone the re-evaluation for a couple of years in view of the expected new evidence that was about to become soon available. Indeed, most of the new evidence generated by the European Communities became available between 1999 to 2002. The European Communities would like to ask JECFA if this has ever happened in other cases. The European Communities has never understood what would have been the problem if its request for postponement were taken into account.

The European Communities notes that JECFA and Codex do not reply to the second part of the question. In any case, it is surprising that the same JECFA Secretariat, which used to be common with

that of Codex, is now not proposing to review again these hormones, despite the wealth of the new evidence that became available from so many sources and the standing request by the European Communities.

It is also noteworthy that the CCRVDF did not adopt the 1999 assessment of the three natural hormones by JECFA, which may mean that this 1999 assessment is of no relevance for the purposes of these disputes.

As regards MGA, the European Communities has requested its re-evaluation on the basis of more recent scientific evidence.

Q19. What would be the procedures for requesting JECFA to re-evaluate its recommendations in light of new concerns/evidence? How would an amendment be adopted? Has the European Communities approached JECFA for this purpose with respect to the hormones at issue in this case? [see Exhibit EC-63]

EC Comments

The European Communities notes the statement by JECFA that the "European Union has not asked the JECFA Secretariat to bring their data referred to in the report of the 11th session of CCRVDF (see below point 1 of question 20) before JECFA for review." This is not correct because there is a standing EC request to review the hormones on the basis of the latest information available, including that generated by the European Communities.

Q20. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones, which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by CCRVDF? What is the status of these recommendations? [see para. 96-97 of EC Rebuttal Submission (US case), para. 79-80 of EC Rebuttal Submission (Canada case)]

EC Comments

The European Communities refers the Panel to its submissions and in particular Exhibit EC-63, which provides a more detailed account of the events with precise references to the original letters. It is unfortunate that JECFA states that it "decided to re-evaluate previous assessment when the Committee is made aware that there is new data which may be pertinent to the risk assessment of the substances in question", but failed to wait for the most important part of these data to become publicly available.

The European Communities draws the attention of the Panel to the statement that "most of the studies were the same", which confirms the EC position. The European Communities also notes that "a complete dossier submitted to the US Food and Drug Administration" was provided and that the "FDA kindly permitted the FAO expert to the Committee to search all their relevant files for data." This statement confirms again the EC position that the US and JECFA could have provided the same data also to the European Communities as it has been consistently requesting.

JECFA states that it performed "a more detailed thorough review of the validity of the analytical methods used in the studies and used only data generated using valid methods. It also performed more detailed statistical and graphical analyses of the data." However, since most of the data were the same old data, one wonders what kind of thorough processing JECFA now did, which it had failed to do in

its 1988 assessment of the same data. This is all the more crucial given that the data in question are unpublished data of the 1970s. The European Communities recalls that this so-called "thorough review" seems to have been performed by Dr. Arnold, who has himself declared to this Panel during the selection procedures that he believes eating meet treated with these hormones poses "no increased health risk for consumers".

JECFA also states that "a few additional investigational studies were also reviewed", but it does not explain which ones and how important they were for its assessment. JECFA further states that "since the FAO FNP 41/12 monograph provides all raw data used (in graphical form) and all the calculations performed, the document is also more transparent than the corresponding monograph produced by the 32nd Meeting". The European Communities reiterates that it precisely has been claiming for transparency in the JECFA proceedings, and a graphical presentation of the same old data is not what one would normally understand by transparency.

JECFA states that "this conclusion was based on studies of the patterns of use of estradiol for growth promotion in cattle, the residues in animals, analytical methods, toxicological data from studies in laboratory animals, and clinical findings in human subjects." The European Communities disputes that such detailed studies have been performed and reiterates its standing request to be given access to these data or to be made available to the Panel and its experts for review.

JECFA further states that "at its 52nd meeting in 1999, estradiol-17β was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-50 ng/kg bw on the basis of the NOEL of 0.3 mg/day (equivalent to 5 μg/kg bw per day) in studies of changes in several hormone-dependent parameters in postmenopausal women. A safety factor of 10 was used to account for normal variation among individuals, and an additional factor of 10 was added to protect sensitive populations." This confirms that (i) JECFA did not consider residues in meat from animals treated with these hormones for growth promotion purposes, (ii) it based its ADI on "changes in several parameters in postmenopausal women" but not on the much lower rates of prepubertal children (as did the European Communities), and (iii) it sought to address these problems with the application of safety factors!

The European Communities notes that statement of JECFA that "the 52nd JECFA performed a detailed theoretical intake assessment based on a worst case scenario (all animals are slaughtered at the time of the highest hormone levels - this time point differs largely from the time point at which the benefit due to the anabolic effect is greatest). In this assessment intake estimates for preferential meat eaters were performed on the basis of the hormone levels of treated animals in comparison with the corresponding levels in untreated animals and the additional "burden" or "excess intake" was calculated. For total estrogens the highest excess intakes from approved uses calculated this way were in the order of magnitude of 30 – 50 ng/person/day. This range of intake is less than 2% of the ADI for estradiol-17β established by JECFA at the 52nd meeting. For certain experimental studies carried out with experimental combinations resulted in an excess intake of around 4% of the ADI." The European Communities would like to see the original of these underlying data, as the similar or more detailed studies and experiments in has generated itself provided different and in many cases much higher values (see e.g. Exhibits EC-16, 17, 18, 19, 34, 47, 52, 53 and 78). The same applies for testosterone and progesterone.

JECFA states that "hormone concentrations found in individual populations of treated animals, although they were typically statistically significant higher than untreated controls, were well within the physiological range of these substances in bovine animals. The data assessed and the worst case scenario calculations made indicated a wide margin of safety of consumption of residues from animals treated in accordance with good practice of use of the veterinary drugs containing the hormones in question. JECFA therefore concluded that there was no need to specify numerical

maximum residue levels for the three hormones and recommended MRLs not specified in bovine tissues." This is an important statement that needs to be factually substantiated. The European Communities notes that the hormone concentrations found in untreated animals were significantly higher than in untreated animals.

As for the reasons for which JECFA established in 1999 ADIs, the European Communities notes the statement that this was due to "the additional data reviewed and the need to establish an ADI as quantitative estimate for a safe oral intake. The exposure assessment performed would then allow the comparison of the estimated intake with the ADI." Thus, this confirms the EC position that it was the new evidence showing risk of cancer that led JECFA review its 1988 assessment. And if JECFA postponed its assessment until the new and more recent data generated by the European Communities were taken into account, it could have reached still another and arguably more accurate conclusion. In any case, it is clear that in 1999 JECFA did not establish ADI in order explain better its evaluation, as it is claimed erroneously by Dr. Boisseau (see his reply to Panel question to the experts no 18).

JECFA states that "sufficient new data from observations in humans were available to the 52nd JECFA which were suitable to derive ADIs." The European Communities does not know and has not seen these "data from observations in humans" and, if they exist, they are certainly different from the data it has generated itself with its own studies. JECFA should therefore provide them to the parties, the Panel and its experts for review. Moreover, the so-called "wide margin of safety" claimed by JECFA to exist is no longer credible in view of the "significantly higher levels" identified in treated animals and the need to establish ADIs, not to mention their direct genotoxicity and the other adverse effects established by the European Communities. Furthermore, the EC scientists rightly question why MRLs were not established in 1999, given that JECFA had felt nevertheless the need to establish ADIs. Was it for the alleged "wide safety margin" or simply because "of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle", as JECFA had admitted in 1988? But if the latter was the real reason, this means that JECFA did not carry out a quantitative dose-response assessment of residues in meat from treated animals under realistic conditions of use, as it is argued by the European Communities.

Q21. What is the mandate of the International Agency for Research on Cancer?

EC Comments

The European Communities has no specific comment at this time.

Q22. Who are the members of the IARC?

EC Comments

The European Communities has no specific comment at this time.

Q23. What are IARC Monographs? How are they prepared?

EC Comments

The European Communities notes the IARC statement that "when the epidemiological evidence is *sufficient,* the final evaluation is *carcinogenic to humans,* regardless of the experimental evidence. In other cases, the mechanistic and other relevant data are considered to determine whether the default evaluation should be modified, upwards or downwards. A subgroup of experts in cancer mechanisms assesses the strength of the mechanistic data and whether the mechanisms of tumour formation in experimental animals can operate in humans. The overall evaluation is a matter of scientific judgement, reflecting the combined weight of the evidence."

The European Communities would like further clarifications on the following points: Does the above statement mean that a substance can be classified in Group 1 even if there are no or a limited number of experiments showing genotoxicity in vivo? Moreover, in which of the different groups are genotoxic substances classified? How does IARC define genotoxic substances?

Q24. Please briefly explain the groupings that are used to categorize "potentially carcinogenic agents"? What are the implications when an "agent" is placed in one of the IARC categories?

EC Comments

The European Communities would like to request the following clarifications: 1) Would the IARC describe its assessments as risk assessments or as assessments that also include risk management? 2) When a substance is placed in Groups 1, 2A and 2B, what is the majority of IARC's members normally expected to do? To authorise or prohibit the substances in question? On what else does their decision depend? 3) Is the assessment performed by IARC a qualitative or a quantitative assessment of potential risk? 4) Is the IARC classification of various groups based on dose-response estimations under realistic conditions of use of the various substances? 5) Is the classification based only on experimental data in animals and extrapolations to humans or do they include also data from residues which such substances may leave in food?

Q25. Which of the six hormones at issue in this dispute (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate) have been evaluated by the IARC? Have any specific risks from the consumption of meat from cattle treated with these growth promotion hormones been assessed by the IARC?

EC Comments

The European Communities notes the statement that "Trenbolone acetate, zeranol, and melengestrol acetate have not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with these growth promotion hormones", and would like the following clarifications: 1) Does it mean that IARC's evaluation of the three natural hormones covers also the specific risks from the consumption of meat from cattle treated with those hormones for growth promotion? 2) Can the IARC be more specific on the last part of the question? 3) Is it possible a pharmacologically active substance that is classified in Group 1 to ever lead residues in food of this substance to be classified into a different category? 4) If so, under what conditions can this take place?

Q26. How does the work of the IARC feed into the work of national regulatory agencies or international bodies, in particular with respect to assessments of risks from the consumption of meat from cattle treated with the six growth promoting hormones at issue in this dispute?

EC Comments

The European Communities would like IARC to clarify what it means by "as scientific support for their actions"? Does it mean that they can be used as risk assessments? Are they normally scientifically complete and adequate to be used as risk assessments? Could IARC be more specific and reply to the last part of the question concerning the consumption of meat from cattle treated with the six hormones or at least for the three hormones that it has assessed and classified?

ANNEX F-3

COMMENTS BY THE EUROPEAN COMMUNITIES TO THE COMMENTS BY THE UNITED STATES AND CANADA ON THE REPLIES OF THE SCIENTIFIC EXPERTS TO QUESTIONS POSED BY THE PANEL

(12 July 2006)

Introduction and general comments

1. The European Communities thanks the Panel for the opportunity to comment on the other Parties' comments on the Panel's experts' replies. Before setting out its comments the European Communities would like to make two preliminary remarks of a general nature.

2. First, the European Communities notes that the United States, in its comments, has chosen to follow its own structure in what may well be considered a full-fledged additional submission. Apart from the fact that reference is made to legal claims which the United States has not made anywhere (e.g. Article 5.6 of the *SPS Agreement*, see paragraph 5 of the US submission), the European Communities considers that this approach is confusing and of little assistance to the Panel and its experts as well as to the other parties. It is not surprising that the US has resorted to this tactic, as the replies of the majority of the experts support the scientific evidence and the arguments of the European Communities.

3. In order to facilitate a structured debate, the European Communities will try to disentangle the misleading comments made by the United States. Also, for the same purpose, the European Communities makes but one set of comments, which addresses the Canadian and (as best as possible) the US comments following the order of the questions as asked by the Panel to the experts and the international bodies.

4. Second, in light of the other Parties' comments on this general issue, it seems appropriate to briefly come back to the role of experts in these panel proceedings. As the European Communities has pointed out in earlier submissions (in particular in its submission of 15 March 2006), the purpose of the scientific questions and the role of the experts is to help the Panel understand the scientific issues involved. Neither the Panel nor the experts should aim to conduct their own risk assessment or to conduct a *de novo* review of the sanitary risks identified by the European Communities. The task of the scientific experts is to assist the Panel in assessing whether the scientific basis of the measure taken by the European Communities complies with the recommendations and rulings of the DSB in the *EC – Hormones* case. But the experts should not make comments on risk management options, since this is not their expertise or role. Therefore, the focus of the scientific questions should be to help the Panel understand the risk assessment conducted by the European Communities since the adoption of the Panel and the Appellate Body reports in 1999. Unfortunately, as the European Communities has demonstrated by its comments of 30 June 2006, the replies of Dr. Boisseau and Dr. Boobis have not always complied with the above requirements.

A. GENERAL DEFINITIONS

Q1. Please provide brief and basic definitions for the six hormones at issue (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate), indicating the source of the definition where applicable.

5. The United States and Canada have not referred to or commented in substance on the experts' (Drs. Boisseau, Boobis and Guttenplan) replies to this question.

Q2. Please provide definitions for the following terms as they relate to the hormones at issue, indicating the source of the definition where applicable: anabolic agents, steroids, steroidal oestrogens, parent compounds/metabolites, catechol metabolites, mitogenicity, mutagenicity, androgenic/oestrogenic activity, genotoxicity, genotoxic potential, carcinogenicity, and tumorigenicity. In your replies, please be sure to identify and describe any relevant differences between the terms.

US comment

6. The United States has not referred to or commented on the experts' (Drs. Boisseau, Boobis and Guttenplan) replies to this question.

Canada's comment

7. The comments by Canada (at paras. 8-9) are not accurate. The statement that a substance (in this case oeastradiol-17β) "has genotoxic potential" does not mean that there is a "statistically likelihood" that it is carcinogenic (this is not what the European Communities has argued) but that on the basis of the evidence available, in particular *in vitro* studies, the genotoxicity of the substance is possible. This is not a theoretical statement but a frequent conclusion scientists make for this type of substances. In addition, in this case there is also *in vivo* evidence supporting that statement. Dr. Boobis and Canada may not like this evidence or would like to see more *in vivo* evidence before they are convinced, but this is irrelevant. The European Communities is entitled to rely on this recent and credible evidence if necessary to achieve its level of health protection.

B. RISK ASSESSMENT TECHNIQUES

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

US comment

8. The US comments on Question 3 are contained in paragraph 13 of its submission. The European Communities notes that there is general agreement among the parties that there is no internationally agreed risk assessment technique, within the meaning of Article 5.1 of the *SPS Agreement*, for the assessment of these hormonal substances. It is equally uncontested by all that there exists a number of documents which represent at most a practical understanding among some international experts on certain principles. These documents do not have any legal value under the *SPS Agreement* since they are not "risk assessment techniques developed by the relevant international organisations." In any event, the European Communities notes that neither the US nor the experts claim that the European Communities has not followed these.

Canada's comment

9. Canada's comments (in particular at paras. 14-15) do not accurately describe the legal relevance of the documents to which it and JECFA have referred to. Canada states that many of the risk assessment techniques and methodologies "are also relevant to the risk assessment of veterinary drugs". However, these are no risk "assessment techniques" in the first place, in the sense of Article 5.1 of the *SPS Agreement* and, secondly, they cannot be applied by analogy to other kind of substances than for those for which they have been foreseen.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological

assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)].

US comment

10. The US comments on the experts' replies to this question are contained in paragraph 13 of its submission. As stated above, these documents reflect the general discussion in the absence of an internationally agreed risk assessment technique and the presence of certain guidance documents. However, the United States misquotes Dr. Boisseau when pretending that he was referring to the "assessment of such drugs "[i.e. the hormonal substances in question] when stating that "it has been internationally harmonised through scientific conferences …". Dr. Boisseau was not referring to the assessment as such, but to a "general rationale" on that assessment. Indeed, if there is some understanding among certain scientists on a general way of conducting a risk assessment, the European Communities applies this as much as any other country.

Canada's comment

11. Canada maintains that, despite of the accuracy of the relevant EC statement "any suggestion that relevant risk assessment techniques or guidance developed by international organizations for the conduct of veterinary drug risk assessments do not exist is baseless".

12. In the European Communities' view, Canada is misinterpreting the replies of Dr. Boisseau and Dr. Boobis. First, it should be underlined that both experts (and in addition Dr. Guttenplan) have confirmed the accuracy of the EC statement. Second, the existing general JECFA guidelines to which Drs. Boisseau and Boobis refer can not be taken – as Canada does – as a replacement of an international detailed Codex standard which alone would be of legal relevance under the *SPS Agreement*.

13. JECFA might have produced certain internal guidelines on risk assessment for certain substances. However, it is a totally different matter to elevate internal JECFA papers, which have never been approved by Codex Members, into the rank of an international standard. Thus, Canada's insinuation and interpretation of the replies by Dr. Boisseau and Dr. Boobis is inaccurate and unacceptable.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) and explain how they differ.

US comment

14. The United States has not provided comments on the experts' (Drs. Boobis, Boisseau, Cogliano, Guttenplan) replies to this question.

Canada's comment

15. In summarizing the experts' replies, Canada reproduces Dr. Boobis' response and presents this as the common denominator of the experts. However, there are differences. For instance, in respect of the "risk assessment" Dr. Boobis introduces a concept of the "weight of evidence", which is not found in the replies by Dr. Boisseau, Dr. Cogliano or Dr. Guttenplan. These experts rather emphasize the risk assessment as an evaluation of risk (Dr. Guttenplan), a description of the "adverse effects of exposure of hazardous agents (Dr. Cogliano) or the "likelihood and the gravity of any unexpected unwanted effect for the consumer" on the basis of "scientific date, relevant with regard to assessing this risk" (Dr. Boisseau).

16. These differences are important since Dr. Boobis' reply, which obviously suits Canada best, implies a margin of discretion in (or balancing and weighing of) the scientific risk assessment procedure, based on the "weight of evidence", which is not the case for the other experts.

17. Furthermore, as regards the risk management step, Canada again uses the language of Dr. Boobis reply and tries to "present" it as the common view of all experts. This is, in particular, interesting since Dr. Boobis refers in this context to "ensuring fair trade" which is not mentioned by any of the other experts. Instead, these experts refer to the use of other scientific criteria such as "economical, sociological, cultural" (Dr. Boisseau) or "legal mandates, technical feasibility, cost, equity, and social norms" (Dr. Cogliano). This is an interesting difference, because the concept of "fair trade" is not clearly defined and Canada and Dr. Boobis may have a different interpretation of this concept than for instance the United States, the European Communities or other experts.

18. Moreover, Canada claims that all experts appear to support the so-called "functional separation" between risk assessment and risk management (at para. 20). Even if this were so, *quod non*, this is irrelevant for the *SPS Agreement*, because the Appellate Body has interpreted correctly its provisions in the 1998 *Hormones* case to partially overlap (at para. 181 of its report).

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

US comment

19. The United States refers to the experts' replies on this question in paragraph 14 of its submission trying to make again the erroneous point that the European Communities risk assessment did not engage in a hazard characterization because it did not evaluate a dose-response relationship. This is discussed in more detail below under Question 11.

Canada's comment

20. Canada's summary of the experts' replies (Drs. Boisseau, Boobis and Guttenplan) concerning "hazard identification" is not accurate. According to Canada, "the experts" agree that hazard identification "involves the determination of *whether* an agent has the potential to cause adverse effects" (Emphasis added). However, this is not what Dr. Boisseau, Dr. Boobis and Dr. Guttenplan say. All of them do not define this step as to "whether" or not there are adverse effects. Rather, Dr. Boisseau, Dr. Boobis and Dr. Guttenplan define hazard characterization in respect of the identification of the different elements causing adverse health effects in humans.

21. In respect of the "hazard characterization" it is not true, as Canada summarizes it, that all experts refer in their definition to a "dose-response assessment" or the determination of thresholds, i.e. an NOAEL or an ADI. Indeed, Dr. Guttenplan merely refers to the "quantitative and/or qualitative evaluation of the nature of the adverse health effects associated with the hazard" without referring to a dose-response relationship or the establishment of whatever threshold. But even Dr. Boobis or Dr. Boisseau clearly condition the dose-response threshold aspects to "whether or not this is possible". Consequently, Canada's implied conclusion that these elements form an "integral part" of the risk assessment which the EC failed to complete are a serious mischaracterization of the experts' replies.

22. As regards the definition of the "exposure assessment" Canada, again, does not provide a proper summary of the experts' replies even though it pretends that all experts have the same view. Canada uses the words of Dr. Boobis to define the exposure assessment as a step to evaluate

"quantitatively" the exposure of consumers to veterinary drugs.[1] However, Dr. Boobis and Dr. Guttenplan refer explicitly not only to the quantitative aspects, but also to the "*qualitative* evaluation of the likely intake".

23. In respect of the "risk characterization" Canada again generalizes from one expert reply and presents them as a common reply of all experts. This is obvious when Canada quotes Dr. Boisseau's statement whereby risk characterization "is not to assess qualitatively and quantitatively the likelihood and gravity of the adverse effects of consumers (…) but to protect consumer's health from any adverse effect associated with residues". In this context, Canada also pretends that all experts confirm that an MRL would be established. This presentation is simply wrong. In fact, neither Dr. Boobis nor Dr. Guttenplan refer to the "protection of consumer health from any adverse effects" and to the establishment of MRLs. Rather, both experts limit themselves to the qualitative and, where possible, quantitative determination, including attendant uncertainties, of the likelihood of occurrence or severity of potential adverse health effects. It follows, therefore, that Dr. Boisseau's reply contains a subjective judgement and a procedural step which is not supported by Dr. Boobis and Dr. Guttenplan, contrary to what Canada pretends. Moreover, Canada persists in its error to consider that it is the "probability" of occurrence of the adverse effect that counts, when the Appellate Body has clarified in the *Hormones* case that it is not the probability but the likelihood (or possibility) that is meant by Annex A(4) of the *SPS Agreement*.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations, in your view, addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? Have they been addressed in the 1988 and 1999 JECFA risk assessments of these hormones? [see Canada's comments in para. 72 of its Rebuttal Submission]

US comment

24. The United States refers to the experts' replies to this question in paragraphs 15, 16 and 17 of its submission. Here again the US refers selectively to the "experts" views, when only Drs. Boisseau and Boobis appear to support what the US is arguing. Moreover, the basic error of these scientists, of the US (and Canada for this matter) and of JECFA is that they all argue that oestradiol is not genotoxic but acts only through hormone-mediated receptors. On the basis of this erroneous assumption, based on old and outdated data, they all come to the conclusion that there is a threshold dose below which there was no appreciable risk over a lifetime of exposure.

25. This kind of statement by the US is surprising given that its own scientists no longer agree with this assertion. The US Carcinogenesis Report since 2002 has classified oestradiol as a proven human carcinogen (see Exhibit EC-101). Indeed, the above US report states *inter alia*:

> "The evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor. *In addition, there is evidence that other mechanisms may play a role in the carcinogenic effects of estrogens in some tissues.* Prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. *Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and*

[1] Canada and Dr. Boisseau, however, differ on the food basket which according to Canada contains 300g muscle, whereas Dr. Boisseau refers to 500g muscle.

> *possibly direct and indirect genotoxic effects.* The relative importance of each mechanism is likely a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state (Yager and Liehr 1996)." (emphasis added)

It is clear from the above excerpt that all the relevant US scientific institutions that have collaborated in the preparation of this Report have come to the conclusion that oestrogen acts not only through the estrogen receptors but, in addition, also by "other mechanisms". The report states also that "the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects". This finding was made for the first time in the 2002 Report and is being repeated ever since. It is very strange that neither Dr. Boisseau nor Dr. Boobis commented on this, and it is even stranger that neither of the defending parties have ever said something about this, which clearly supports the EC assessment on this crucial point. Indeed, the European Communities is not doing other than what Dr. Boobis has described in his reply to Question no 7, namely that: "In practice, it is likely that as veterinary drug residues in food are avoidable by not using the drug, the Committee would have declined to establish an ADI".

Canada's comment

26. The European Communities is again opposed to Canada's selective perception of the experts' replies. Canada merely pretends that "the experts confirm that JECFA was aware of "non-linear situations" and took these into account in conducting its risk assessment for the hormones at issue".

27. However, Dr. Boisseau's reply is more nuanced than Canada would like to see. Dr. Boisseau replied that JECFA was aware in 1987 of non-linear situations but this was a general comment. In its reply, Dr. Boisseau only exemplifies this general awareness in respect of specific substances which are unrelated to the hormones in dispute and where at the time, JECFA concluded not to establish an effect-dose relation or to recommend an ADI.

28. Yet, in respect of oestradiol-17β, Dr. Boisseau expressly states that "in its 32nd session held in 1987, JECFA did not address this kind of non-linear situation for oestradiol-17β (…)". Similarly, in 1999, according to Dr. Boisseau, JECFA "did not take into account consideration a non-linear situation in its risk assessment (…)". Against this background, Canada's presentation of Dr. Boisseau's reply on non-linear situations is unsustainable.

29. Canada finds support in the statement of Dr. Boobis. But his statement and that of JECFA are scientifically unsound for the reasons already explained by the European Communities. Canada claims (at para. 31) that the European Communities has presented no evidence; however, this is not true because the evidence is there but Canada chooses to ignore it. For instance, Canada did not comment so far on the 2002 US Carcinogenesis Report quoted above.

Q8. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please identify and describe any steps that are taken in the risk assessment process to build a margin of safety into the final recommendation.

US comment

30. The United States does not refer to or comment on the experts' replies to this question nor to JECFA's and Codex replies to the same question (question 10 in questions asked to Codex, JECFA and IARC).

Canada's comment

31. Canada's description of the expert replies demonstrates again a lack of precision and accuracy. Canada, for instance, refers to Dr. Boobis answer (to Question 54) that an ADI is a threshold "that will pose zero risk" to human health. However, in this reply, Dr. Boobis only refers to a WHO definition of an ADI whereby there would be "no appreciable risk with daily exposure over a lifetime". It goes without saying that the difference of "no risk" and "no appreciable risk" is considerable since the latter one involves a subjective judgement. Indeed, what may be "appreciable" to somebody may not be "appreciable" to others. Yet, in this sensitive hormones' discussion, these fine differences make a difference. This is an issue of risk management, not of risk assessment, in the sense that Dr. Boobis cannot decide for the democratically elected governments in the European Communities what risk is "appreciable". It is, therefore, necessary to make the Panel aware of such rather blunt presentations of the experts' replies by Canada. Indeed, Canada is confusing its own subjective (policy) judgements with the remarks of the scientific experts.

32. It may not come as a surprise that Canada's description regarding the experts' replies on MRLs is also misleading. First, it is inaccurate to say that "the experts have confirmed that the MRL is a management tool (…)" and that "if residues are within the MRL, then the ADI is unlikely to be exceeded and no adverse effects to human health are to be expected". First, only Dr. Boisseau refers in its answer to MRL but not the other experts. Second, Dr. Boisseau clearly states that a MRL is "an operational tool which offers a practical way to be sure that this ADI will not be exceeded". Conversely, contrary to what Canada describes Dr. Boisseau does not say "no adverse effects to human health are to be expected". Rather it appears that at this stage one would have to go back to the discussion whether an ADI poses "no risk" or "no *appreciable* risk". Moreover, Canada states (at para. 36) that JECFA has built into its calculations large safety margins. However, none of the points made by Canada here is correct, at least not in the case of these hormones. First, because JECFA did not consider all the metabolites for instance of oestradiol, like the esters. Indeed, *Maume et al.* have confirmed the presence of estradiol **esters** in meat of treated animals in an order of magnitude not very different to the free estradiol residues. But the estradiol esters is a totally new class of residues that have not been considered before in any risk evaluation. Their potential bioactivity may be much higher than the bioactivity of estradiol as such. The recent data provide clear evidence (1) for their existence after application of estradiol to cattle and (2) for their elevated oral bioactivity. Undoubtedly, these are important new data, and an accurate evaluation of the risk originating from steroid hormone esters will only be possible, if many more data become available. This includes the additional need to look for trenbolone esters and their bioactivity. (see *Maume D, Deceuninck Y, Pouponneau K, Paris A, Le Bizec B and Andre F (2001): Assessment of estradiol and its metabolites in meat, APMIS, **109**:32-38,* Exhibit EC-47*).* Second, because the bioavailability of these hormones has been seriously underestimated, and thirdly, because the so-called food basket can easily lead to residues intakes that by far exceed the endogenous production of these hormones, especially by pre-pubertal children.

Q9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

US comment

33. The United States refers to Drs. Boisseau's and Boobis' and to JECFA's replies to this question in paragraph 17 of its submission.[2] The US approves the statement by Dr. Boisseau about the quality and the quantity of the data used by JECFA. However, this is not surprising because the data

[2] Question 11 in questions asked to Codex, JECFA and IARC.

used by JECFA are too old. Conversely, the data used by the European Communities are more recent and converge on this point with the statement of the US Carcinogenesis report which states that "… Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects ...". Thus, there is no doubt that there are several gaps in our knowledge but the new evidence available confirms the direct and indirect genotoxicity of oestradiol and of the other hormones.

Canada's comment

34. Canada draws conclusions from JECFA's replies which are plainly wrong. JECFA was making a general and abstract statement on this point, but this tells us nothing of whether the ideal situation described in its reply is applicable in the case of these hormones, because JECFA's evaluations date from 1988 and are too old by today's scientific evidence.

Q10. In para. 129 and 168 of its Replies to the Panel Questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not". Does Codex have risk management options other than (1) the establishment of an MRL, (2) establishing that an MRL is not necessary or (3) no recommendation?

US comment

35. The United States does not refer to or comment on Dr. Boisseau's and on Codex' and JECFA's replies to this question.[3]

Canada's comment

36. The European Communities observes that, like the question itself, Canada's comments are confusing again what is a risk management measure in the terminology of Codex Alimentarius and JECFA and what this term should be understood to include in the *SPS Agreement*, as interpreted by the Appellate Body in the *Hormones* case.

Q11. What should, in your view, be the components of a qualitative risk assessment, compared with a quantitative risk assessment? [see para. 82 of Canada Rebuttal Submission]

US comment

37. The United States does not refer to or comment on the experts' (Drs. Boisseau, Boobis, Cogliano) replies to this question.

Canada's comment

38. Canada draws (at paras. 42-43) from the replies of the two scientists (Dr. Boisseau and Dr. Boobis) to this and to subsequent questions the conclusion that a risk assessment that does not include a dose-response assessment would be incomplete. However, as the other scientists who replied to these questions have explained, the European Communities has performed a qualitative (and where possible a quantitative) dose-response assessment. Moreover, Canada criticises (at para. 43) the relevance of the monographs produced by the IARC as a basis for conducting a dose-response assessment and cites in support the 1998 Appellate Body report in the *Hormones* case. However, the statement by the Appellate Body quoted by Canada is partly incorrect and partly irrelevant today. It is

[3] Question 12 in questions asked to Codex, JECFA and IARC.

incorrect because the evaluation of substances by IARC, like the three natural hormones, have served for so many years responsible governments in their risk assessments and it is simply inaccurate and scientifically unsound to suggest that they do not provide a sufficient basis for a risk assessment. This is because the toxicological and other scientific evidence on which both the JECFA and the IARC base their findings is the same: they both decide on the carcinogenicity of a substance on studies conducted *in vitro* and *in vivo* and extrapolate from animal models to humans (if there is no direct evidence from experiments on humans). There is nothing in the JECFA data base and the methodology used by it which is different from the data on carcinogenicity and the methodology used by IARC. This is very important to understand. If there are residue data from meat treated with these hormones for animal growth promotion, IARC will use them in the same way as JECFA normally does. The difference is that JECFA has come to the conclusion that the three natural hormones are not genotoxic, which is not the conclusion reached by IARC on the basis of broadly the same toxicological evidence. But once JECFA had reached the conclusion that there is a safe threshold, it then used the residues data from treated meat in order to see if the presumed safe theoretical threshold would be exceeded. This, the IARC did not have to do, as the other direct and indirect evidence it examined supported the characterisation of these hormones as proven human carcinogens. Moreover, the most recent data cited and used by the European Communities and also those cited (for the first time) in the 2002 US Carcinogenesis Report confirm that oestrogen is genotoxic by direct and indirect mechanisms of action. Therefore, the data from residues in treated meat, to which para. 200 of the 1998 Appellate Body report refers, are irrelevant.

39. It should however be stressed that, in any case, the 1999, 2000 and 2002 risk assessment conducted by the European Communities were based also on residues in meat treated with these hormones for animal growth promotion purposes, which were generated under realistic conditions of use, that is where GVP is respected but also where abuse or misuse could occur. These studies have shown that the resulting residues in treated meat are by far higher than the residue levels considered by the old and outdated studies on which the defending parties and JECFA based their findings. Moreover, the intake of residues from treated meat consumed by prepubertal children would exceed the ADIs and MRLs established by JECFA if the much lower levels of endogenous production of the three natural hormones is taken into account. That is why the European Communities considers imperative that these old data and the methods by which they have been measured and assessed should be provided to this Panel, its experts and the European Communities for a review. It is only then that a proper conclusion could be drawn on the accuracy and relevance of these old data for the risk assessment.

Q12. How is scientific uncertainty addressed in risk assessments in general? With respect to the assessment of risks from the consumption of meat treated with the growth promotion hormones at issue, how has scientific uncertainty been considered by JECFA/Codex ? How does it differ from the way it has been considered by the European Communities in its assessment of risks from the consumption of meat treated with the growth promotion hormones at issue?

US comment

40. The United States while referring to Dr. Boobis' reply to this question in paragraphs 17 and 20 of its submission[4] does not discuss or comment the issue of scientific uncertainty.

Canada's comment

41. Canada makes again (at para. 46) the irrelevant argument that the European Communities is not consistent because it prohibits hormone-treated meat but allows the consumption of foods (e.g.

[4] There is no reference to Dr. Boisseau's reply to the same question.

milk, eggs, meat) containing some of these hormones at levels many times higher. But this argument has been made by both parties before the 1997 panel and has been rejected clearly by the Appellate Body in the 1998 Hormones report (at para. 221) as "an absurdity". So the European Communities wonders why Canada keeps repeating it.

C. ASSESSMENT OF OESTRADIOL-17B

Q13. To what extent, in your view, does the EC risk assessment identify the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol-17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice? To what extent does the EC risk assessment evaluate the potential occurrence of these adverse effects?

US comment

42. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan) replies to this question in paragraphs 19, 20, 21, 32, 37 and 84 of its submission. However, the underlying theme in all US comments is the fundamental error that these hormones, and in particular oestradiol 17β, are not carcinogenic because a safe threshold exists. This is a fundamental error on which the European Communities has already commented above (e.g. to Question no 7).

Canada's comment

43. Canada's statement that the replies by Dr. Boisseau, Dr. Boobis and Dr. Guttenplan all indicate that the EC risk assessment "was deficient in one manner or another in its evaluation of the potential occurrence of adverse effects" is a very unqualified summary. In particular, Dr. Guttenplan has expressly stated that the European Communities has done a "thorough job in identifying the potential adverse effects on human health of oestradiol-17β" and that the European Communities has "performed thorough studies of residues levels in cattle, and the environment". Most importantly, Canada states (at paras. 49-51) that "there is no evidence that this [genotoxic] potential is realized in vivo (as opposed to in vitro)", that Dr. Boisseau disagrees with the European Communities "as do most other experts and international scientific bodies", and that the European Communities decision not to conduct a complete risk assessment "is not supported by the evidence". None of these statements is correct. The European Communities has shown that there is sufficient and constantly growing evidence from studies *in vivo* that show the direct genotoxicity of oestradiol 17ß and its catechol metabolites in animal and human tissue as well as the mutagenicity of oestradiol 17ß metabolites in experimental animals:

- Li et al. (2004) have demonstrated that the N7-guanine adduct (N7Gua) and the N3-adenine adduct (N3Ade) of E2-3,4-quinone (the putative carcinogenic E2 metabolite) were present in the DNA of the mammary gland of ACI rats after injection of 4-HO-E2 or E2-3,4-quinone (Exhibit EC – 121).
- Markushin et al. (2003) have detected the N3Ade (and in part N7Gua) adducts of 4-HO-E2 and 4-HO-estrone (E1) in the breast tissue of women (Exhibit EC – 118).
- Chakravarti et al. (2001) demonstrated mutations in the H-ras gene of SENCAR mouse skin after topical application of E2-3,4-quinone, and Chakravarti et al. (2003) found similar mutations in the mammary gland of ACI rats after administration of E2-3,4-quinone. The type of mutations in both *in vivo* animal systems can be explained by depurination of the N3Ade adducts. These experiments are reviewed in Cavalieri et al. (2006) (Exhibit EC – 48).

- Cavalieri et al. (2006) used the Big Blue® rat model to assess the mutagenicity of E2 and 4-HO-E2 *in vivo* and found both compounds to be mutagenic. The mutational spectrum observed for 4-HO-E2 was consistent with the formation and depurination of N3Ade adducts (Exhibit EC – 125)

44. It should be noted that the magnitude of DNA adduct levels and mutagenic activities reported in these studies is not very high and seems to be much lower than encountered with most known genotoxins, which indicates that oestradiol may be a weak genotoxin. This may also be true for the other hormones and this may explain why standard genotoxicity assays show negative or borderline effects with these compounds. Moreover, the genotoxic activity of oestradiol 17β and its metabolites determined in rodent assays *in vivo* may be obscured by the diet, which usually contains high concentrations of phytoestrogens, e.g. from soy. It has been recently reported that several phytoestrogens induce the enzyme quinone reductase, which inactivates the quinones of catechol estrogens and thereby reduces DNA damage (Bianco et al., 2005, Exhibit EC – 124)).

45. The question, therefore, is not that there is no evidence of genotoxicity *in vivo*, but rather how much evidence more is needed by the defending parties before they would be forced to reconsider their views, as did JECFA and Canada recently in relation to other substances, e.g. for Carbadox.

Q14. In your view, does the risk assessment undertaken by the European Communities on oestradiol-17β follow the Codex Guidelines on risk assessment, including the four steps of hazard identification, hazard characterization, exposure assessment, , and risk characterization with respect to oestradiol-17β?

US comment

46. The United States refers to the experts' (Drs. Boobis, Boisseau and Guttenplan) replies to this question in paragraphs 19, 20 and 32 of its submission. In paragraph 19 of its submission, the United States claims that "the experts' responses confirm that, while the EC Opinions engage in hazard identification, the first step of a risk assessment, the Opinion fail to complete any of the remaining three components." The European Communities disagrees with the selective citation and the biased conclusions drawn by the US. Dr. Guttenplan has certainly supported the EC position on this point.

Canada's comment

47. Canada's presentation that "Drs. Boisseau, Boobis and Guttenplan also agree with Canada that the EC failed to follow the Codex guidelines on risk assessments" and that "[t]he experts share Canada's concerns that the EC (and SCVPH) took significant and unjustified short-cuts in the conduct of its risk assessment" is plainly wrong.

48. Neither Dr. Boisseau nor Dr. Boobis or Dr. Guttenplan make any specific comments on Canada's concerns. Thus, to present the experts' replies as if these had said: "Yes, Canada is right" is, to say the least, wishful thinking.

49. More specifically, Dr. Boisseau's position can hardly be described as being "very critical of the EC's decision not to follow the Codex guidelines" as Canada presents it. Dr. Boisseau has explicitly stated that "[T]he European Communities does not indicate anywhere in its submission that it does not intend to follow the Codex guidelines on risk assessment including the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization. On the contrary, the following indicates that the European Communities considers the same approach for assessing the risk associated with the residues of growth promoters." On that basis, how is it possible for Canada to describe Dr. Boisseau's position as "very critical on the EC's decision not to follow Codex guidelines"? Just the opposite is true.

50. While it is true that Dr. Boisseau at the end of his reply has put in brackets a comment whereby "[t]hese two statements call for refining the exposure assessment of hormones residues" it is a complete mischaracterization by Canada to interpret this statement as a criticism that the European Communities should "not abandon the entire risk assessment methodology" and, even more, to take this conclusion as a confirmation of Canada's submission. Again, this is little more than wishful thinking by Canada.

51. It is no surprise that Canada's comment on Dr. Guttenplan's reply is also more than selective. Canada refers to Dr. Guttenplan's alleged criticism on the European Communities' hazard characterization and risk characterization "for the same reasons advanced by others". The European Communities is wondering who are these others and on what basis Canada can make such an unqualified statement.

52. On substance, Canada also completely ignores that Dr. Guttenplan has expressly stated that the "EC has been thorough in following Codex guidelines on hazard characterization and very thorough in exposure assessment." This indeed invalidates directly Canada's own statement whereby the "EC has done very little that resembles an exposure assessment".[5] In this context, the European Communities is also surprised about Canada's description that the European Communities has admitted "that it did not, because it could not conduct an exposure assessment". The paragraph 141 of the EC rebuttal submission quoted by Canada does not support this statement.

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

Q15. Does the identification of oestradiol-17β as a human carcinogen indicate that there are potential adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes? Does your answer depend on whether good veterinary practices are followed? [see paras. 206-207 of EC Rebuttal Submission (US case), para. 121 of EC Rebuttal Submission (Canada case), paras. 97-98 of EC Replies to Panel Questions, para. 76-77, 150 and 155-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission]

US comment

53. The United States refers to the experts' (Dr. Boobis, Boisseau and Guttenplan, Cogliano) replies in paragraphs 34, 38, 42 and 43 of its submission. Conveniently, the United States does not comment on Dr. Boisseau's categorical statement regarding the dependence of his reply on the efficient implementation of good veterinary practices.

Canada's comment

54. From the outset, it should be noted that none of the experts "agree with Canada" on the effect of the carcinogenicity of oestradiol-17β. Indeed, none of the experts take any position on any statement made by Canada.

55. Canada's blunt summary of the experts' replies whereby "most of the experts conclude affirmatively that there would be "no appreciable risk" of adverse effects from exposure from this one minimal source of oestradiol 17β" is inaccurate as the experts differ considerably in their replies and most of them agree with the EC position.

[5] See Canada's comments on expert replies, para. 54.

56. Dr. Boisseau merely says that "oestradiol-17β (…) is not likely to produce adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes". Yet, what is "likely" or not appears to be quite a subjective judgement. Moreover, even Dr. Boisseau explicitly subjects this view to the respect of good veterinary practices as otherwise all the work "to protect human health with regard to veterinary drug residues is meaningless".

57. Dr. Cogliano explicitly states that "the identification of oestradiol-17β as a human carcinogen indicates that there are potential adverse effects on human health when oestradiol-17β is consumed in meat from cattle treated with hormones for growth promotion purposes." This statement hardly supports Canada's theory that the consumption of beef treated with oestradiol-17β does not entail an "appreciable risk".

58. Furthermore, Dr. Guttenplan states that "if potential is taken to mean possible, then an adverse effect cannot be ruled out, but it is unlikely if good veterinary practices are followed". As Dr. Boisseau, Dr. Guttenplan thus refers to the likelihood of adverse human health effect. Yet, as can be seen from his reply (and it is also interesting to contrast this reply with Dr. Boisseau's), such an assessment contains a subjective judgement which justifies that in case of a political decision to take "zero risks" even the slightest minimal chance should be excluded. This is even more justified in this specific case where there are considerable doubts about whether GVP are always respected and which even according to Dr. Boisseau would render all the assumptions "meaningless".

59. Finally, Canada argues that the EC evidence demonstrates that "multiple hormone implants resulted in residues that were still less than the ADIs." However, the data generated by the EC study in question (by *Daxenberger et al. 2000*) documented that the residues after improper use would exceed by far the ADIs.

Q16. Does the scientific evidence relied upon in the SCVPH Opinions support the conclusion that carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity? [see para. 148 of the EC Replies to Panel Questions and paras. 35-40 and 46 of US Rebuttal Submission]

US comments

60. The United States refers to the experts' (Drs. Boisseau, Boobis, Guttenplan) replies to this question in paragraphs 34, 36 and 50 of its submission. While pretending that all experts confirm the view that no scientific evidence supports the conclusion that the carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity, the United States has to admit, in the same paragraph (34) that Dr. Guttenplan has taken a much more nuanced view on this issue. The United States' interpretation of other statements made by Dr. Guttenplan, which allegedly suggest, that he links the carcinogenic effects to the hormonal activity, are simply erroneous. The European Communities has explained several times (also above in relation to question 13) that in 2002 there was sufficient evidence from experiments in vivo and this evidence is still growing further. In addition, there is evidence for the mutagenicity of oestradiol-17β as determined in cell culture. For example, Kong et al (Int. J. Oncology, 17: 1141-1149, 2000) reported on the mutagenicity of oestradiol-17β in V79 hamster ovary cells and recently Zhao et al., in a paper whose authorship included Dr. Guttenplan himself (Chem. Res. Toxicol. 19: 475-479, 2006, Exhibit EC-110), reported the mutagenicity of the 4-OH catechol metabolite of oestradiol-17β in BB Rat2 embryonic cells. In this study, multiple treatment of the cells with 50 to 200nM 4-OH oestradiol-17β induced mutations in the BB Rat2 cells in a dose response fashion, with a significant increase being observed after 3 and 3 treatments at the 200nM level. The mutational spectrum resulting from 4-OH oestradiol-17β treatment was different than the "background" mutations seen in the control (untreated) cells further supporting the conclusion that the mutations were in fact caused by the 4-OH catechol estrogen. 2-OH oestradiol-17β did not induce mutations. These results support the difference in carcinogenicity difference

between these 2 catechol metabolites and differences in their ability to cause transformation of normal human breast epithelial cell line MCF-10F as reported by Russo, et al. (J. Steroid Biochem. Mol. Biol. 87: 1-25, 2003, Exhibit EC-115). Furthermore, these results are particularly significant in that the 4-OH catechol metabolite of oestradiol-17β has been detected in the mammary tissue of mice in a model where mammary tumorigenesis is dependent on the presence of estradiol (Devanesan et al. Carcinogenesis, 22: 1573-1576, 2001 (Exhibit EC – 122); Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003, Exhibit EC-90) and in human breast tissue (Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003, Exhibit EC-90).

61. With regard to the study by Chakravarti et al (Oncogene, 20; 7945-7953, 2001, Exhibit EC-48), which is criticised by Dr. Boobis, it should be explained that it detected mutations in the H-*ras* gene in the skin of SENCAR mice following dermal treatment with E2-3,4-quinone, with the specific nature of the mutations detected being consistent with the expected depurination of adenine due to the formation of an E2-3,4-quinone-Adenine adduct. This is relevant to the potential mutagenicity of estradiol in humans because: First, we know that oxidative metabolism of oestradiol-17β to the E2-3-4-quinone metabolite occurs in human breast tissue because E2-quinone adducts to glutathione have been detected (Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003, Exhibit EC-90). Second, adducts of the E2-3,4-quinone with ademine and guanine have been detected in the mammary tissue of ACI rats injected into the mammary gland tissue with 4-OH E2 or E2-3,4-quinone (Carcinogenesis, 25:, 289-297, 2004, Exhibit EC-121). These findings are ignored by Dr. Boobis as well as by the US.

Canada's comment

62. Unlike the US, Canada criticizes Dr. Guttenplan's support for the EC conclusion on the basis that he has not made an analysis on its own. However, Canada has obviously no difficulties in relying on Dr. Boisseau who, in turn is merely invoking (old) JECFA reports and who, therefore, has also not made an analysis on its own. Canada thereby applies a double standard just as it sees fit for its own purposes. In any case, the European Communities has explained above that Dr. Guttenplan has published together with other scientists several papers in peer-reviewed journals, the most relevant one a few months ago (Chem. Res. Toxicol. 19: 475-479, 2006, Exhibit EC-110) which has used the Big Blue® rat model to assess the mutagenicity of oestradiol-17β and 4-HO-E2 *in vivo* and found both compounds to be mutagenic. The mutational spectrum observed for 4-HO-E2 was consistent with the formation and depurination of N3Ade adducts.

Q17. Could you comment on Canada's statement that "the studies commissioned by the European Communities also failed to find evidence of "catechol metabolites" – that is the oestradiol metabolites identified as the source of the genotoxic potential – in meat from treated animals"? What would be the implication of an absence or presence of catechol metabolites? [see para. 102 of Canada Rebuttal submission, EC Exhibit 51A]

US comment

63. The United States refers to Drs. Boisseau's, Boobis' and Cogliano's replies to this question in paragraph 44 of its submission and very conveniently omits any reference to Dr. Guttenplan's straightforward reply.

64. Furthermore, its reference to Dr. Cogliano's reply is misleading as Dr. Cogliano does not conclude "that detectable levels of catechol metabolites were not formed from the parent compound", but rather concludes that "*the absence of catechol metabolites could imply either* (1) [the above] *or* (2) that some level of catechol metabolites was formed that the test methods were not sufficiently sensitive to detect it." (emphasis added) Indeed, as the EC has explained above (in relation to question no 13), there is sufficient and constantly growing evidence from studies *in vivo* that show the direct

genotoxicity of oestradiol 17ß and its catechol metabolites in animal and human tissue as well as the mutagenicity of oestradiol 17ß metabolites in experimental animals.

65. It should be noted that the magnitude of DNA adduct levels and mutagenic activities reported in these studies may not be very high. It seems indeed to be much lower than encountered with most known genotoxins, which indicates that oestradiol may be a weak genotoxin. However, this can also be true for the other hormones and this may explain why standard genotoxicity assays show negative or borderline effects with these compounds. Moreover, the genotoxic activity of oestradiol 17β and its metabolites determined in rodent assays *in vivo* may be obscured by the diet (Bianco et al., 2005, Exhibit EC-124).

66. Finally, that oestrogen may be genotoxic by direct or indirect mechanisms of action is now admitted even by the US since its 2002 Carcinogenesis Report, cited above, and any argument now to the contrary by the US is necessarily not credible.

Canada's comment

67. Canada takes issue with Dr. Guttenplan on the amounts of catechol metabolites by referring to "other experts'" confirmation. However, since Canada does not identify these other experts this is a rather unqualified remark. On substance, the European Communities finds it remarkable that Canada does not criticize Dr. Guttenplan's statement that even "the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity".

68. Moreover, the European Communities would emphasize that, in the absence to the contrary, Canada obviously agrees with Dr. Cogliano's statement whereby "the presence of catechol metabolites would support the potential for adverse effects to occur. The absence of catechol metabolites could imply either (1) that detectable levels of catechol metabolites were not formed from the parent compound or (2) that some level of catechol metabolites was formed that the test methods were not sufficiently sensitive to detect it." This is the most likely explanation, as stated above.

Q18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol-17β is genotoxic. Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see paras. 118-119 of EC Rebuttal Submission (US case), paras. 123-124 of EC Rebuttal Submission (Canada case), paras. 87-91 and 153-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission, and paras. 90-97 of Canada Rebuttal Submission]

US comment

69. The United States refers to Drs. Boobis' and Cogliano's replies to this question in paragraphs 35 and 44 of its submission and very conveniently omits to refer to Drs. Boisseau's and Guttenplan's replies. The latter's reply certainly does not "confirm" - as the United States claims (at paragraph 35) – "that the scientific evidence cited by the EC in its Opinions does not support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones." Quite to the contrary, Dr. Guttenplan confirms the existence of such evidence and states that "the evidence now is much stronger" citing a study of 2004.

70. Moreover, the US argues (at para. 36) that the European Communities has failed to explain why its evaluation of estradiol 17β was not subject to a CVMP guideline requiring confirmation of an in vitro positive using an appropriate *in vivo* assay. This comment is disingenuous because the pharmaceutical industry, the defending members and JECFA, i.e. those arguing that these substances are safe, should produce the evidence showing that estradiol 17β is not genotoxic *in vivo*. The EC has fulfilled its obligations by funding a number of studies and also by collecting the growing evidence

from experiments *in vivo* showing the direct genotoxicity of these hormones, in particular of estradiol 17β. It is now high time that the US (and Canada) stops criticising the European Communities for absence of evidence which itself did not have when it approved these hormones more that 30 years ago and makes an effort to prove what it preaches, that is that these hormones are not genotoxic by direct action. Instead of criticising the European Communities on the basis of purely hypothetical assumptions, the US should have tried to explain the statement from its 2002 Carcinogenesis Report which states:

> "The evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor. *In addition, there is evidence that other mechanisms may play a role in the carcinogenic effects of estrogens in some tissues.* Prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. *Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects.* The relative importance of each mechanism is likely a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state (Yager and Liehr 1996)." (emphasis added)

Canada's comment

71. Canada's interpretation of Dr. Boisseau reply is quite astonishing. First, Canada tries to construe from Dr. Boisseau's reply a difference for a substance having "genotoxic potential" and being "genotoxic". Yet, nowhere in his reply does Dr. Boisseau address this issue so that Canada can hardly take this response as support for its own theory. Moreover, Canada describes Dr. Boisseau's reply on the establishment of an ADI by JECFA in 1999 as "pointing to the need to place exposure to oestradiol 17β from this source into context." It will remain Canada's secret what it means by such a description, since Dr. Boisseau instead submitted that the ADI was established "in order to present in a more convincing way the outcome of its [JECFA's] assessment".

72. In respect of Dr. Boisseau's reply it is also difficult to see how Canada can claim support for its assumption that oestradiol 17β is not genotoxic *in vivo*. He does not say so in his reply to Question 18 and even Dr. Boisseau's reply to Question 13 does not contain such a general statement.

73. The comments by Canada (at paras. 72-73) are subject to the same criticism mentioned above for the statements made by the US. Indeed, the UK VPC constitutes quite a remarkable evolution on this point from its previous evaluation of these hormones in 1995, and it is certainly less categorical in its findings (it uses the terms "is likely") than Canada. Even so, however, the statement quoted by Canada (at para. 72) contrasts sharply with the findings in the 2002 US Carcinogenesis Report quoted above by the European Communities, which Canada has chosen to ignore.

Q19. The European Communities states that "... it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance". Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case), paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]

US comment

74. The United States refers to the experts' (Drs. Boobis, Boisseau, Cogliano, Guttenplan) replies to this question in paragraphs 37 through 40 of its submission. Its reading of Dr. Guttenplan's and Dr. Cogliano's replies is erroneous. On Dr. Guttenplan, the United States claims that he does not take a clear view on whether oestradiol 17β is genotoxic at level found in residues in meat from cattle treated with growth promoting hormones. However, this is not what Dr. Guttenplan has said.

75. On Dr. Cogliano, the United States' claims that he "concurs [with Dr. Boobis] "noting that the EC's statement regarding the lack of a threshold has not been demonstrated by the scientific evidence." Quite to the contrary, however, Dr. Cogliano said: "The EC's statement that a threshold cannot be identified reflects their view of genotoxic mechanisms, just as the contrary statement that there is a threshold and that this threshold is above the levels found in meat residues reflects how Canada and the US view genotoxic mechanisms. Neither statement has been demonstrated by the scientific evidence, rather, they are different assumptions that each party uses in their interpretation of the available evidence."

Canada's comment

76. Canada's statement that Dr. Boobis' and Dr. Cogliano's replies would support its own argument that for substances endogenously produced by human body there must be threshold is, at least, a challengeable conclusion. Indeed, neither Dr. Boobis nor Dr. Cogliano, who apart from this question obviously have a different perception about the genotoxicity of these hormones, do at all address this argument. Canada makes (at para. 74) the rhetoric argument that "humanity would have been wiped out by cancer millennia ago". This statement is highly unscientific. First, humanity did not use to eat meat treated with hormones, save for approximately the last 30 years and this only in the US (and a bit later in Canada). Secondly, the rates of cancer in general (including prostate and breast) are increasing, in particular in the US, where they are higher by about 20% compared to those in Europe. Third, as the European Communities has explained above, it may be that these hormones are weak carcinogens, which explains why they could not be detected by the old and most of the existing assays. But the rates of cancer observed today are a serious cause for concern. Furthermore, the implication of the Canadian claim that a substance that is produced endogenously cannot be carcinogenic when administered exogenously is incomprehensible.

77. The same applies for Canada's claim (at para. 75 and 76) that even EFSA has recognised safe thresholds for genotoxic substances. This is simply not true because the EFSA opinion cited by Canada, although issued for another purpose, simply states that the incidence of cancer may not be increased, but it does not state that there is no risk from such substances.

78. Canada states (at para. 74) "that experts from around the world" contradict the EC' claim, but it manages to cite only the UK VPC and the JECFA reports. These are the "experts around the world". Canada fails however to cite the well known reports from the IARC – which as its name indicates is the best placed international institution on issues of cancer research and prevention – nor does Canada pay any attention to the US Carcinogenesis Report.

79. It is clear from the replies of the experts that they are divided on this issue (2 against 2), but if the expected replies of the other 2 experts are added, then the majority of the experts agrees in substance with the EC position.

Q20. In your view, how do the European Communities' conclusions above relate to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary"? To what extent,

in your view, has JECFA's conclusion that oestradiol "has genotoxic potential" affected its recommendations on this hormone?

US comment

80. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) and JECFA's (to a related question)[6] replies to this question in paragraph 41 of its submission. The European Communities disagrees with the summary of the statements made by the US in that paragraph. That oestradiol 17β is carcinogenic by both direct and receptor mediated mechanisms is no longer in doubt (see the latest article by Cavalieri et al., 2006, see Exhibit EC-125). This has been stated also by the US since its 2002 Carcinogenesis Report to which the US fails to refer.

Canada's comment

81. Canada draws an unjustified conclusion from the experts' replies whereby "Drs. Boisseau, Boobis and Guttenplan all consider the EC's conclusion about the absence of thresholds to be inconsistent with the Codex standards." Yet, the answers of these experts are much more nuanced than Canada presents. For instance, Dr. Boisseau only states that the "European Communities' conclusions are questionable". It goes without saying that there exists a difference between "inconsistent" (as Canada qualifies it) and "questionable". The same applies to Dr. Boobis who submits that the "EC conclusion on the absence of safety at any level of exposure is somewhat at odds with the underlying basis of the Codex conclusion regarding the need for an ADI or MRL". Again, if something is "somewhat at odds" it does not mean that it is "inconsistent". Finally, Dr. Guttenplan merely states that the European Communities' conclusions above are "at variance" with those of Codex. It is difficult to see how this can be reconciled with Canada's statement that the EC's conclusions are "inconsistent" with Codex standard.

82. In this context, it is also an unqualified assumption by Canada that "to the extent that most of the experts found the EC conclusions on the matter are unsupported by the evidence and are "questionable", they support the existing Codex standards." Indeed, the mere comparison between a Codex standard and a respective EC conclusion does not lend any support whatsoever about the value of this standard.

83. Finally, the European Communities would take issue with Canada's unsupported conclusion that the "experts' answers also confirm that even though JECFA acknowledged that oestradiol 17β has "genotoxic potential", this acknowledgment did not generate concern about the safety of the substances and therefore did not affect its recommendation". Indeed, none of the experts makes any qualified statement to this effect and Canada's inference from the experts' replies is therefore completely baseless. At most, Dr. Boobis stated that "I do not believe that JECFA's conclusion that oestradiol has "genotoxic potential" affected its recommendations on this hormone (…)". As can easily be seen this is a mere unsubstantiated guess and personal opinion by one expert whereas the other experts remain mute on this issue. Thus, Canada's presentation is far from being an objective description of the facts.

84. What is even more important is that the statements by Dr. Boisseau and Dr. Boobis are partial because they do not consider the totality of the available evidence, such as that mentioned by the European Communities and in particular the reports from the IARC and the US Carcinogenesis Report which have been made available to them. Dr. Boobis concentrates only on the JECFA reports, which are based on very old data.

[6] Question 20 of the questions asked to Codex, JECFA and IARC is about …

Q21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential? Does your answer depend on whether good veterinary practices are followed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see, *inter alia*, the SCVPH Opinions and paras. 63, 83, 89-91 and 93 of US First Submission, paras. 131-136 of Canada Rebuttal Submission]

US comment

85. The United States refers to the experts' (Drs. Boobis, Guttenplan and Boisseau) replies to this question in paragraph 50 of its submission. Overall, the experts' replies are much more nuanced than what the United States suggests when claiming that they all "confirm that the scientific materials cited by the EC in its Opinions do not demonstrate or support the conclusion that any of the five hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity." As both Dr. Boobis and Dr. Guttenplan report, there are some data that indicate the possibility of genotoxic effects. The data are probably not "conclusive" (Dr. Guttenplan) and perhaps not "convincing" (Dr. Boobis) to everyone, but it is more than a sufficient and legitimate basis for a legislator acting on the basis of precaution to adopt provisional measures.

Canada's comment

86. Canada's blunt statement that "Drs. Boisseau, Boobis and Guttenplan all refute the EC's claims about the potential genotoxicity of the other five hormones" is not supported by the experts' replies. For instance, Dr. Boobis merely states that "there is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic". However, what is "convincing evidence"? In the same vein, Dr. Guttenplan refers to "no conclusive evidence" or "some evidence that certain of the hormones have genotoxic potential". Yet, what is "conclusive" or what means "some evidence"? Whatever it means, it can in any case not justify Canada's unqualified conclusion that there is no "potential genotoxicity of the other five hormones". Rather, their statements confirm the EC position that there are considerable gaps and uncertainties in our knowledge, which justify applying Article 5.7 of the *SPS Agreement* in order to achieve ones chosen level of health protection.

Q22. How would you define *in vivo* DNA repair mechanisms? How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat? Does your answer depend on whether good veterinary practices are followed in the administration of these hormones? To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones? Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why? [see paras. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission]

US comment

87. The United States refers to the experts' (Drs. Boobis, Guttenplan) replies in paragraph 31 of its submission. The US again misrepresents the views of the scientists, in particular those of Dr. Guttenplan, who stated *inter alia* that "a small fraction of damage inevitably escapes repair" and that consideration of this issue by the SCVPH is in fact irrelevant to the debate (even though he found some references in the SCVPH assessment that discussed this issue).

Canada's comment

88. Canada spends again a number of paragraphs (at paras. 85-89) trying to interpret the experts' replies as supporting its views on this question. But as Dr. Guttenplan has explained in his reply, there is no reason to believe that the repair mechanism in the case of these hormones would be different from what is happening in other instances. It is also inevitable that some DNA damage will remain unrepaired, as is the case with so many other direct genotoxic substances. As the 2002 US Carcinogenesis Report states: *"… prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression…[and that]…the relative importance of each mechanism is likely to be a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state"*. This means that to go down the road advocated by the defending parties and Dr. Boobis, i.e. in trying to estimate how much of the DNA damage is likely to be repaired in time and what would be the carcinogenic potential of the damage left unrepaired would not be possible in view of so many specificities involved, supposing one could undertake this kind of estimation in a reliable way. That is why Dr. Guttenplan states that this issue is irrelevant for the debate on the genotoxicity of oestradiol and whether an ADI for such substances could or should be fixed.

Q23. To what extent is it necessary or possible to take into account the "long latency period" of cancer in the conduct of a risk assessment, which is supposed to assess carcinogenic effects of these hormones when consumed in meat? Have the hormones in dispute been used as growth promoters over a sufficient number of years for an assessment of their long-term effects on human health to be made? [see para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case)].

US comment

89. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) replies on this question in paragraphs 57 and 58 of its submission.

90. In Footnote 127 the United States is suggesting that there is no evidence of adverse effects after more than 20 years of consumption of beef from cattle treated for growth promotion purposes. However, as Dr. Boobis rightly concludes "... a negative result from such an observational study would not resolve the issue."

91. Furthermore, the United States misinterprets Dr. Guttenplan's statement that "hormones in meat [...] have now been consumed for a sufficient number of years to observe strong or moderate increases in risk." The United States pretends that Dr. Guttenplan hereby suggest that there is no such evidence. However, the European Communities does not interpret in the same way Dr. Guttenplan's statement, quite the opposite.

Canada's comment

92. Canada summarises the replies of the scientists in a partial way in paragraphs 90-93 to come to the conclusion that "… exposure to residues of hormones in meat from treated animals is only a small fraction of the overall exposure to the substance from a variety of sources, including that produced endogenously within the human body ...". A careful reading of the replies of the scientists however does not support this conclusion. Indeed, none of the scientists explicitly said that the exposure is only "a small fraction", because it is not easy to estimate the level of the residues. For instance, the 2002 US Carcinogenesis Report simply stated that the use of these hormones for growth promotion increases the level of residues to above "their normal levels". The point therefore is that the two scientists cited by Canada have not and could not have come to the conclusion that the residues is

a small fraction, not least because they do not know it and could not prove it (because of the background and other confounding factors).

Q24. To what extent is it possible to identify possible co-founding factors causing cancer and attribute them to identified sources? What are the implications of these factors for the conduct of a risk assessment evaluating the adverse affects caused by residues of growth promoting hormones in meat? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

US and Canada's comments

93. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) replies on this question in paragraph 59 of its submission and Canada in paragraphs 94-96. They both appear to accept (as do all the scientists) that there is now an association established between meat consumption and cancer, but they dispute that the evidence is there to clearly establish a causal link between the residues in meat from hormone-treated cattle and the high cancer incidence. But the European Communities has not argued it and does not take issue with the fact that it is difficult to establish that causal link. What is very important to note, however, is that the defending parties cannot make the argument that because the establishment of the causal link is difficult, there should be assumed that such a risk is insignificant or does not exist because the added burden is thought to be small. Furthermore, the defending parties can no longer make their simplistic argument that humans are exposed to hormonal residues from so many other sources, so a small additional exposure from the residues in treated meat would not make any difference. This simplistic argument has been made over and over again by the defending parties to the Panel and it is now clear that there is no scientific basis to this claim because they cannot establish the causal link of what they argue. However, the evidence is there, and it is indeed growing, associating high rates of cancer with meat consumption, and these rates of cancer are higher in the US than in Europe, and one day if the US and Canada would like to find out more about any possible causal link between the two so as to protect their people the same way as the European Communities does, it could undertake the studies which Drs. Cogliano and Guttenplan have suggested.

Q25. To what extent do the three recent studies referred to by the European Communities confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones? Please also comment on the EC statement that one of the studies "was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, which means that the subjects should have been exposed to hormone-free meat in their diet. This may further imply that it cannot be excluded that the risk of cancer may be further increased if meat treated with hormones for animal growth promotion were to be consumed". [see paras. 145-148 of EC Rebuttal Submission (US case) and paras. 139-142 of EC Rebuttal Submission (Canada case), footnote 97 in para. 147 of EC Rebuttal Submission (US case), and Exhibits EC-71, 72, 73]

US and Canada's comments

94. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) replies on this question in paragraphs 61 through 63 of its submission. Contrary to what the United States suggests, the experts are far from "[agreeing] that the three studies demonstrate no such risk." While Dr. Boobis holds this view, both Dr. Cogliano and Dr. Guttenplan, on the contrary, confirm that these studies indicate or suggest risks. Indeed, as the European Communities has explained above, at least 2 out of the 4 scientists seem to agree that this kind of epidemiological evidence could provide indirect information indicating that there may be a causal link.

95. It is therefore surprising the Canadian comment (in para. 102) that the European Communities is "manipulating a genuine scientific interest". This kind of manipulating tactic has been deployed by the defending parties since 1997, in their argument that the risk from residues in treated meat with these hormones is miniscule compared to the higher exposure of humans to intake from other natural foods (meat, broccoli, soya, eggs, etc.), a statement which the Appellate Body has dismissed as "an absurdity" in its 1998 *Hormones* report (at para. 221). Conversely, the EC argument has been supported by at least one panel expert in the 1998 *Hormones* case and appears to be considered relevant by two of the present experts. Indeed, it is recalled that during the 1997 panel report on *Hormones*, one of the experts for the Panel (Dr. G. Lucier) had then stated:

> *"For every million women alive in the United States, Canada, Europe today, about a 110,000 of those women will get breast cancer. This is obviously a tremendous public health issue. Of those 110,000 women get breast cancer, maybe several thousand of them are related to the total intake of exogenous oestrogens from every source, including eggs, meat, phyto-oestrogens, fungal oestrogens, the whole body burden of exogenous oestrogens. And by my estimates one of those 110,000 would come from eating meat containing oestrogens as a growth promoter, if used as prescribed."*

96. However, the Appellate Body in 1998 denied evidentiary value to Dr. Lucier's statement for the reason that his opinion "… does not purport to be the result of scientific studies carried out by him or under his supervision focusing specifically on residues of hormones in meat from cattle fattened with such hormones …". (at para. 198 of the 1998 Appellate Body report).

Q26. Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91]

US comment

97. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan, Cogliano) replies on this question in paragraphs 59, 60 and 63 of its submission. The United States' bold assertion that "the experts' responses confirm that the epidemiological studies cited by the EC in its Opinion fail to identify a link between hormone residues in meat and cancer" is once again a misrepresentation of what these experts actually stated. To take the example of Dr. Boobis, while he does state that "there is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in human," he qualifies that statement in the very next sentence pointing to the existence of "some studies that are consistent with such an association …" (studies which admittedly he thinks have other possible explanations, some of which are more plausible than hormones in meat being causal). In the same vain, Dr. Guttenplan also concedes that "the results are at least consistent with a possible effect of hormones on breast and prostate cancer."

Canada's comment

98. Canada submits that the breast and prostate cancer rates between Europe and North America are "relatively similar". However, on the basis of the figures mentioned by Dr. Boobis the difference would still be around 20% higher in the United States, which can hardly be described as "relatively

similar". In this context, it is also amazing how Dr. Boobis minimizes the potential hormones treated beef on these differences by linking any difference rather to higher meat consumption. Apart from the fact that Dr. Boobis is just engaging in some "best guessing effort", it is undeniable that the higher meat consumption is intrinsically linked to higher hormones consumption. Thus, it defies any logic and common sense, as Dr. Boobis does, to refer to one single figure on consumption but leaving aside the very fact that the higher consumption inevitably entails a higher intake of hormones.

(b) Residue analysis

Q27. How do the residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue?

US and Canada's comments

99. The United States and Canada do not refer to or comment on the experts' (Drs. Boisseau, De Brabander) replies to this question.

Q28. How do the hormones naturally present in animals, meat, or human beings differ from the residues in meat of the three natural hormones used for growth promotion purposes?

US comment

100. The United States does not refer to or comment on the experts' (Drs. Boisseau, De Brabander) replies to this question.

Canada's comment

101. Contrary to Canada's view, Dr. De Brabander's opinion is not "much less clear". Rather, Dr. Brabander is very explicit and detailed in his reply suggesting that the residues in meat of the three natural hormones used for growth promotion purposes are not identical to the hormones naturally present in animals. What is even more questionable is that Canada criticises Dr. De Brabander's statement on the ground that "his position would be inconsistent with the detailed residue evidence reviewed by JECFA in its 1999 residue monograph. The monograph presents detailed data on hormone concentrations in various tissues, including muscle and fat, in untreated heifers and steers. Dr. De Brabander's suggestion in this regard simply does not withstand close scrutiny." Yet, as we know and as JECFA and Codex admitted openly in their replies – including that by Dr. Boisseau – the residue data used by JECFA in 1999 are essentially the same as those used in 1988 and that for the most part they date back to the 1960s and 1970s, whereas those used by Dr. De Brabander are the most recent ones. Therefore, the Canadian claim cannot be taken seriously. The European Communities reiterates once more its claim to the defending parties to provide their residues data and the Panel to request those data from JECFA and make them available to the experts, so that close scrutiny could indeed be exercised.

Q29. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the synthetic hormones found in meat in their assessment of the risks from such residues? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? How do they compare with the MRLs set by Codex? [see paras. 165-176 of EC Rebuttal Submission (US case); pages 55-68 of the Opinion of the SCVPH of 30 April 1999 in US Exhibit 4, para. 144 of US First Submission, Exhibits US-6 and 7, footnote 46 of US Rebuttal Submission]

US and Canada's comments

102. The United States refers to the experts' (Drs. Boisseau, De Brabander) replies to this question in paragraphs 90, 91 to 93 of its submission. The US criticises Dr. De Brabander's reply as not being based on concrete evidence. The US further cites Dr. Boisseau as stating that "…older data is neither irrelevant or "bad" data simply due to its age. Rather, it is the quality and quantity of data that is important, and for the hormones at issue, a great deal of high quality data exists." As a general statement, the European Communities surely agrees with it. However, as regards the data on MGA used by JECFA date from the 1960s and 1980s, they are industry studies not published in any peer-reviewed journal, and have not been seen by anyone else except the US and JECFA (see Exhibit EC-127). Moreover, as long as these parties refuse to make them available for verification, it is legitimate for an expert and the European Communities to question their scientific quality and credibility, given that the more recent data produced by the EC studies and those available in open literature do not support the conclusions which the defending parties and JECFA pretend to draw from those old data.

103. For these reasons, it is very inaccurate and misleading the comment made by Canada (at para. 111) that the methods used by JECFA are "modern" and validated ones. The problem is not only whether they are modern and validated but whether the residues which they are supposed to measure, if the MRLs were to be adopted one day by Codex Alimentarius, are taken with these modern methods or in the 1960s and 1980s when these so-called "modern" methods did not even exist. This is the point. Indeed, Canada (and the US) unjustifiably and incorrectly criticise the reply by Dr. De Brabander because he made his point as follows: "*At the time they are [the residues] produced (1987) there were no analytical methods available to quantify these residues at that concentration level in a correct way (methods as GC-MS-MS or LC-MS-MS)"*. It is obvious, therefore, that Canada's comment (at para. 111) that "…his cursory conclusion is in stark contrast to the extensive evaluation of residue data conducted by JECFA. In particular, recent residue data from studies using "modern" validated methods (HPLC-MS, GC-MS and LC-MS) were assessed in the JECFA Residue Monograph for the 58th Meeting. All ten studies cited date from 1999 to 2002" is inaccurate because: First, JECFA in 2000 did not carry out any extensive evaluation of the data, it simply took for granted the old and unpublished data of the pharmaceutical industry; second, the ten studies cited in the 58th meeting of JECFA are those that will be used if the MRLs for MGA proposed by JECFA will be accepted one day in the future by the Codex Commission, but they are clearly not those used to generate the data in the 1960s and 1970s.

104. Moreover, Canada's summary of Dr. Boisseau's reply is misleading. Dr. Boisseau not merely stated that the SCVPH did not conduct a quantitative assessment but rather states more accurately that "[a]s, in its 1999 report, SCVPH concluded "that no threshold level and, therefore, no ADI can be established for any of the six hormones" (including the three synthetic ones), *there was no need for SCVPH* to conduct a quantitative assessment (…)." (Emphasis added). Obviously, it makes a difference if the SCVPH, as Canada insinuates, failed to do a quantitative assessment or, as Dr. Boisseau states there was a very good reason for SCVPH not to do such an assessment.

Q30. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the three natural hormones in meat in their assessment of the risks from such residues? Is it possible to compare these to the ADIs recommended by JECFA in 1999? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? [see paras. 120-123 and 155-164 of EC Rebuttal Submission (US case), pages 33-54 of 1999 Opinion in Exhibit US-4, para. 144 of US First Submission, and 52nd JECFA Report in Exhibit US-5]

US and Canada's comments

105. The United States refers to Dr. Boobis' reply to this question in paragraph 90 of its submission. No reference is made to Dr. De Brabander's reply. As the European Communities has noted in its comments of 30 June 2006 on Dr. Boobis' reply to this question, his position is incorrect because the SCVPH did perform the comparison of the ADI and MRL values proposed by JECFA with those generated by the EC studies that were reviewed by the SCVPH. In addition, the reply of Dr. De Brabander confirms the EC finding that the data used by JECFA are old and their validity can be questioned, until we are given the means to see and review them. The comment by the US (in para. 90) on the reply of Dr. Boobis is misleading, because it seems that both have not understood that JECFA reviewed old data that did not take into account realistic conditions of use of these hormones, unlike the data generated by the EC studies for the first time and examined by the SCVPH. Dr. Boobis asks the rhetorical question that "the frequency of occurrence of such misuse" is not stated. However, the studies cited at Exhibits EC-65, 67, 68, 69, 70 and 70-73 show that the higher the frequency the higher the risk will be. But in the case of prepubertal children the EC studies have clarified explicitly that even a unique occurrence or an occasional one would be sufficient to lead to residue levels in meat that would exceed by many times their endogenous production of these hormones.

106. Since Dr. Boisseau referred back in his answer to this Question to his reply to Question 29, the same criticism on Canada's summary of Dr. Boisseau's statement applies here.

Q31. Please comment on the US statement that "concentrations of oestradiol-17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of oestradiol-17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." In your reply please take into account the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels" and the statement by the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered. [see paras. 51 and 144 of US First Submission and Exhibits US-6 and 7, para. 98 of EC Replies to Panel Questions, Exhibit EC-101, and para. 2.3.2.3 of the 1999 Report of SCVPH]

US comment

107. The United States refers to Dr. De Brabander's reply to this question in paragraph 96 of its submission. No reference is made to Dr. Boisseau's reply. The United States comments on the view taken by Dr. De Brabander that "there is no need to add more [hormonal substances] by artificial ways" stating that this is Dr. De Brabander's "personal opinion or policy statement." As a matter of fact, Dr. Boisseau seems to take the opposite view by referring to a "theoretical" of "no additional intake of residues [being] acceptable." What both experts express here, is indeed a policy statement, a policy statement of the kind the European Communities as a risk regulator has every legitimacy to make.

Canada's comment

108. In its comments to the experts' replies, Canada again demonstrates its very selective perception of what the experts actually said. While it quotes *in extenso* Dr. Boisseau (who may be understood to support Canada's position) it basically ignores Dr. De Brabander's very critical remarks regarding the significant increase of estradiol-17β in human food if all animals were treated

accordingly. The Panel would be well advised to take good note of Dr. De Brabander's response and to draw its own conclusions why Canada is unwilling or unable to comment on the serious questions in relation to animal welfare, environment and consumer protection as raised by Dr. De Brabander.

109. More importantly, however, Canada resorts (in paras. 116-117) to its dear and old argument (in the absence of anything else) that "…in order appropriately to understand the risks associated with the use of growth-promoting hormones, one must view the exposure to these hormones in their overall context, including the wide exposure to natural hormones from other dietary sources and endogenous production of natural hormones." However, this kind of argument has been clearly rejected by the Appellate Body in the 1998 *Hormones* case as "an absurdity". Moreover, the Appellate Body has also found that the occasional use of meat from pregnant cows or those treated for therapeutical or zootechnical purposes does not lead to arbitrary or unjustifiable discrimination and do cannot undermine the EC's level of health protection (at paras. 222-225 of its report).

Q32. Please comment on the conclusions of the EC risk assessment (Opinion of the SCVPH of April 2002) that ultra sensitive methods to detect residues of hormones in animal tissues have become available but need further validation. What is the significance of this with regard to identifying whether the natural hormones in meat are endogenously produced or are residues of hormones used for growth promotion purposes?

US and Canada's comments

110. The United States refers to Dr. Boisseau's reply to this question in paragraph 93 of its submission. No reference is made to Dr. De Brabander's reply. However, Dr. De Brabander states that "there are now new data available demonstrating that the pattern change of hormones by the application of the 'natural' hormones used for growth promotion purposes." This is in direct contradiction with Dr. Boisseau's statement that ultrasensitive detection methods would be "less useful in the case of the three natural hormones, which are endogenously produced by food producing animals." The United States seems to agree with Dr. Boisseau's comment without, however, commenting clearly on this contradiction. The basic point Dr. De Brabander was making in his reply is that the residue examined by JECFA were generated with the old methods and that new methods should be used now to re-evaluate them. This is in agreement with the position of the European Communities. Dr. Boisseau's reply is besides the point, because the new powerful and ultra sensitive methods will always be required in order to determine the origin of residues in meat, for example in order to determine whether is it endogenous or exogenously administered and whether there was an abuse or misuse.

Q33. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

US comment

111. The United States refers to the experts' (Drs. Boisseau, Boobis, De Brabander) replies to this question in paragraphs 97 through 99 of its submission and also to Codex' and JECFA's replies on

related questions.[7] Contrary to what the United States pretends there is complete dissent among the experts on the reasons why JECFA re-evaluated the three natural hormones,[8] and the Panel is referred here to the reply of JECFA which admits that the ADIs were set because of the new evidence that became available in the meantime.

Canada's comment

112. It is not clear whether Canada's comment is fully consistent with its comment on Question 18. In this question Canada assumes that the "genotoxic carcinogen [of oestradiol] appears to have promoted at least in part JECFA's 1999 re-evaluation", whereas in its comment to Question 18 Canada denied that JECFA's establishment of an ADI was related to its finding about "potential genotoxicity", (see para. 71 last sentence).

113. Moreover, what is interesting is that Dr. Boobis appears to recognise that "in the intervening time from the first to the second evaluation, it became clear that exposure to the natural hormones, albeit at levels appreciable higher than found in meat from treated cattle, could have adverse effects in humans". This is remarkable, as he admits that there is a problem of principle (despite all the talk about eggs, milk and broccoli etc.), and it appears to be rather a question of "how much" is acceptable (see also Canada's comment in this respect at para. 125, last sentence).

114. Canada's comment (at paras. 127-128) apparently approving the explanations provided by JECFA and Dr. Boobis is inadequate. Indeed, after the CCRVDF refused to consider the 1999 re-evaluation of the three natural hormones, where ADIs were considered necessary in order to avoid the risk of cancer identified, the continued 1988 indication that MRLs are not "necessary" do not enable the countries using these hormones to see if the ADIs are reached or exceeded. It would therefore be imperative that JECFA and Codex review again all these hormones soon by taking into account all the latest evidence and data available, in particular, those generated by the studies sponsored by the European Communities.

Q34. Please comment on the EC argument that the 1999 JECFA report based its findings on (a) outdated residues data and (b) not on evidence from residues in meat but on studies with experimental animals and on general studies of IARC. If the data were not new, did JECFA take this into account in its evaluation? What are the implications of using such data for the purpose of conducting a risk assessment? How reliable are extrapolations from animal studies to possible adverse effects on humans? How does this compare with the kind of data and studies used with respect to other veterinary drugs? [see para. 120 of EC Rebuttal Submission (US case), para. 102 of EC Rebuttal (Canada case)]

US comment

115. The United States refers to Dr. Boisseau's reply to this question in paragraphs 49, 92 and 111 of its submission. No reference is made to Dr. De Brabander's reply. The reference to Dr. Boisseau is always the same namely his statement that "the quality and the number of the available data are more important than the dates at which these data have been produced." The European Communities has already commented on this statement, which it considers scientifically unsound (see EC comments on replies to question 34).

[7] Question 20 in questions asked to Codex, JECFA and IARC.

[8] Of course, there is agreement on the outcome of that evaluation, but that is not the question that was put to the experts. The outcome – JECFA finding that these hormones are safe for consumers – is a fact and not a matter of assessment.

116. The US further claims (at para. 111) that "[a]s noted by the United States in its Rebuttal Submission, and confirmed by Dr. Boobis' analysis above, even in the artificial scenarios developed by EC scientists, in most cases extreme misuse and overdosing of cattle with implants did not result in violative residue levels, *i.e.*, levels exceeding ADIs and MRLs." This statement is not correct because the new evidence generated by the European Communities does establish that the ADIs and MRLs will be exceeded by the residue levels resulting from misuse or abuse. Since the US (and on this point also Canada) keep arguing that extreme misuse did not result in violative residue levels, it is important to quote the conclusion from the relevant EC study (Exhibit EC-17) which states:

> "Treatement with zeranol and testosterone propionate, even after multiple application, does not cause any problems, as far as infringement of the threshold levels is concerned. Off-label application of trenbolone acetate and estradiol benzoate, however, may lead to illicit values. Exceeding of the MRL was found in the liver in one out of two animals after 3-fold and in two out of two animals after 10-fold dose of the 200 mg-trenbolone acetate-implant. Estradiol threshold levels were violated in the liver and in the kidney even after 3-fold dose of Synovex-H. Fattening of calves with the preparations Synovex-H and Synovex Plus lead to similar residue levels as after Synovex-H or Finaplix-H treatment of heifers".

117. It is therefore misleading for the US to summarise the findings of the study in the way described above.

Canada's comment

118. Canada completely fails to comment on Dr. De Brabander's reply. Instead, Canada merely looks for support in Dr. Boisseau's answer. However, contrary to what Canada tries to present as "what is generally accepted within the scientific community: that scientific data do not deteriorate simply because the passage of time", Canada would have been well advised to address Dr. De Brabander's statement whereby "[t]he implications of not using such (modern) data is that the results of the risk assessment are biased in favour of the "allowance" of hormones." Indeed, new data obviously may lead to different conclusions and it is, therefore, indispensable to update and review constantly scientific evidence. Canada obviously fails to do so.

119. Furthermore, Canada also misrepresents Dr. Boisseau's answer concerning the assessment of hormones. Dr. Boisseau merely stated that "[f]or assessing the growth promoters, JECFA has used the same procedure it has used for all other veterinary drugs". Re-formulated by Canada this statement reads as follows: "[a]s the experts confirm, *the data* and process used for assessing the safety of hormones are the same as those used for other veterinary drugs" (emphasis added). Thus, Canada just by convenience adds the word "data" and it presents this as a commonly held view by "the experts" even though Dr. De Brabander (as the only other experts replying to this question) did not make such a statement. This is just another example on how Canada tries to manipulate the Panel in its presentation of the experts' responses.

Q35. Please comment on the European Communities claim that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. Is this correct? Have subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies? [see para. 171 of EC Rebuttal Submission (US case), para. 161 of EC Rebuttal Submission (Canada case), para. 55, including footnote 60 of US First Submission and Exhibits CDA-20, 33, 34 and 35]

US comment

120. The United States concedes that the experts (Drs. Boisseau, De Brabander) have confirmed that the studies relied upon date indeed from the 1960s and 70s (paragraph 49 f its submission). The United States relies on Dr. Boisseau's statement cited above (question 34), which the European Communities considers scientifically unsound for the reasons explained above.

Canada's comment

121. Canada ignores Dr. De Brabander's reply for obvious reasons. But Canada appears also to accept that the data examined by JECFA in 2000 and again in 2004 for MGA date from the 1960s and 1970s.

(c) Dose-response relationship

Q36. How would you describe a dose-response assessment? Is it, as suggested by Canada in para. 78 of its Rebuttal Submission, "widely, if not universally, accepted that adverse effects arising from hormonal activities are dose-dependent"? Is dose-response assessment a necessary component of hazard characterization? Or, is there an alternative approach which can replace the dose-response assessment. Is a dose-response assessment feasible/necessary for substances that are found to be genotoxic or to have genotoxic potential? [see para. 153 of EC Replies to Panel Questions, para. 200 of EC Rebuttal Submission (US case); paras. 143, 154, and 156 of US First Submission, paras. 70-74 of US Replies to Panel Questions, and paras. 34 and 37-40 of US Rebuttal Submission; paras. 76-82 of Canada Rebuttal Submission]

US comment

122. The United States refers to Drs. Boisseau's and Boobis' reply to this question in paragraph 21 of its submission. No reference is made to Dr. Cogliano's reply. Contrary to what the United States claims there is no consensus among the experts on whether a dose-response assessment is a necessary component of hazard characterisation. Indeed, Dr. Cogliano takes the exact opposite view. Also, Dr. Boobis recognises that there may be differences in approach between Europe and the US and Canada as regards the assessment of compounds that have been "identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action."

Canada's comment

123. Although all the experts, including the Codex and JECFA, agree that there are no legally binding risk assessment techniques in the sense of Article 5.1 of the *SPS Agreement* for this kind of substances, Canada makes the unsubstantiated statement (at para. 141) that the hazard-based approach would be inconsistent with the obligations under the *SPS Agreement* that a substance be evaluated for the "potential for occurrence" of an adverse effect. The European Communities finds nothing of this sort in the terms "potential for occurrence", as interpreted by the Appellate Body in the *Hormones* case, given also that a qualitative assessment of the risk is also permissible. In any case, the European Communities has carried out such an analysis of the likelihood of occurrence of the scientifically identified risk in the case of these hormones.

Q37. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "...while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents..."? [see Exhibit CDA-25]

US comment

124. The United States does not refer or comment on the experts' (Drs. Boisseau, Boobis) replies to this question.

Canada's comment

125. The European Communities considers that Canada's statement (at para. 142) that "in light of the universally held view that the adverse effects of hormones are dose-dependent", is erroneous because it is factually not true, as the evidence presented by the European Communities has demonstrated. Indeed, except JECFA and the 2 experts Drs. Boisseau and Boobis who participated in the risk assessment of JECFA, the majority view (which is growing steadily since 1999) is that expressed by the IARC and the 2002 US Carcinogenesis Report that these hormones act by direct and indirect mechanisms.

(d) Sensitive populations

Q38. Please describe the range of physiological (or background) levels of the sex hormones in humans and identify the variations in these levels on the basis of age, sex group, and physiological stages.

US comment

126. The United States refers to Dr. Boisseau's reply to this question in paragraph 65 of its submission, in the context of its comments on the replies given on Question 40 (see below).

Canada's comment

127. Canada pretends that Dr. Boisseau in his reply "raises concerns, as many others have done, about the reliance by the EC on a new 'ultrasensitive biosassay'". However, first of all, Dr. Boisseau has not expressed any "concerns" but he merely said that "[i]t would be important to know whether these new bioassays have been properly validated (…)". Thus, Dr. Boisseau has merely raised a question. Second, Canada refers to "many others" while, indeed, all other experts have not raised any concerns. Canada, therefore, is making a misleading general statement, which is not supported by the facts.

Q39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol-17β and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the populations which have been identified as particularly sensitive such as prepubertal children" [see para. 147 of the EC Replies to Panel Questions]

US comment

128. The United States refers to the experts' (Drs. Boisseau, Sippel) in paragraphs 67 and following of its submission. Contrary to what is claimed by the United States, Dr. Boisseau does not state that "the EC has failed to assess this risk entirely." Dr. Boisseau merely takes the view that a quantitative dose-response assessment (as opposed to a qualitative one) would have been needed.

129. The United States discusses Dr. Sippel's reply to this question in great detail (in paras. 64-82). As regards the validation of the Klein assay, the principle of the yeast assay has been validated in an international comparative study of different assays for estrogens (Andersen et al., Comparison of short-term estrogenicity tests for identification of hormone-disrupting chemicals. *Environmental*

Health Perspectives; 107 (Suppl. 1): 89-108, 1999, Exhibit EC-123), so this should not now be in doubt. Moreover, how can the US (and Canada on this point) claim that an assay cannot be used because it had not been properly validated, since it is clear that JECFA used old "historic" values for endogenous hormone levels in children that are clearly and undisputedly wrong because the old assays used (RIA) cannot measure such levels? Therefore JECFA used the LIMIT-OF-DETECTION as the "real values" in children, which is obviously wrong and scientifically unacceptable.

130. The US criticise the EC statement "any excess exposure..." but the concept of concentration additivity has been proven for estrogens, including the demonstration of "0+0 ≈ 0" (i.e. that two doses which alone do not produce any detectable effects, when added together result in an observable effect). Thus, any dose matters. On dose additivity see: Rajapakse N., Silva E., Kortenkamp A.: *Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action*, in Envir. Health Perspec. 110, 917-921 (2002) (Exhibit EC – 116); and also Tinwell H., Ashby J.: *Sensitivity of the Immature Rat Uterotrophic Assay to Mixtures of Estrogens*, in Envir. Health Perspec.112, 575-582 (2004) (Exhibit EC – 112).

131. The US criticises (at para. 67) the reply of Dr. Sippell for "proposing a different result than his own research". However, the cited statement from Dr. Sippell is from a 2000 (published in 2001) study, and a lot has happened since then, including the publication of many of the cited papers. Thus, Dr. Sippell demonstrates his scientific integrity by adjusting his opinion according to the developing scientific research. This is contrary to for example Dr. Boobis, who repeatedly claims that his opinion has not changed since 1999, despite the publication since 1999 of so many papers on direct genotoxic action.

132. At para. 68 the US cites the study by *Schmidt* which shows an overall association between estradiol levels and postnatal breast development for the groups as a whole. But the study also shows large variations in estradiol levels, including a demonstration of breast development without measurable levels of estradiol. This emphasises the difficulty in measuring the very low estradiol levels, and the study clearly shows breast development, likely caused by estradiol, also in girls where the estradiol level cannot be determined by the RIA assay. Whether this is a pathological effect cannot be answered before the possible outcome of perturbed breast development (breast cancer) can be assayed (i.e. in 40-50 years), but recent research into the origin of breast cancer do suggest that changes in mammary gland development may play a significant role (see Baik I, Becker PS, DeVito WJ, Lagiou P, Ballen K, Quesenberry PJ, Hsieh C-C.: *Stem cells and prenatal origin of breast cancer*, in Cancer Causes and Control 15: 517–530, 2004).

133. In para. 69 the US discusses the *Lampit et al* study, which clearly demonstrate an effect of the administrated estradiol on the growth of the children. However, the US criticises that *Lampit et al.*, "fails to quantify the amount of estradiol that would be required to accelerate growth in normal children". However, this is a consequence of the lack of sufficiently sensitive assays, since *Lampit et al.* cannot measure the serum levels of estradiol, neither before nor after the administration of estradiol. Thus, *Lampit et al*. clearly show an effect of administrated estradiol, despite serum levels not reaching the current detection limit of the assays. This is very important and an extremely relevant finding which the US avoids to confront objectively.

134. In paras. 70 and 71 the US advances a number of unscientific arguments. It is textbook knowledge that estradiol strongly influences the onset of puberty in girls. Is this questioned by the US and Canada? Given that it is beyond doubt that estradiol is the main determinant for the onset of puberty in girls, it seems reasonable that Dr. Sippell raises the possibility that exposure to excess hormones in the US may play a role for trends in puberty disorders.

135. In para. 73 the US discusses the other publications cited. But in line with many other publications, the *Felner & White paper* clearly shows that a small amount of estradiol strongly affects breast development in children.

136. The US statement in para. 74 contains many aspects that need clarification. First, there are several publications that show higher estrogen levels for twins (1.7 to 3 times higher in a *twin pregnancy* compared to a singleton pregnancy) (Kappel 1985; TambyRaja 1981; Ikeno 1985). Second, there are many publications showing lower estrogen levels in women with preeclampsia (Goldkrand 1978; Long 1979; Shibata 2000). Thus, in the absence of other risk factors for breast cancer that change in exactly the same way as the estrogen levels do in these groups, it is reasonable to correlate the changes in breast cancer risk to changes in the levels of the most likely cause for the changed risk, and that is the differences in estrogen levels. The US asks for mechanistic evidence. However, there are so many peer-reviewed papers relating breast cancer to estrogens. Moreover, the publication by *Baik et al. 2004* (cited above) provides a possible mechanistic explanation, especially when combined with other publications linking the cells described by *Baik et al*. to cell types that are the prime candidates for being the cells-of-origin for breast cancer (for example, Petersen et al., 2003). See on Estrogen levels in twin pregnancies compared to singletons*:* B. Kappel, K. Hansen, J. Moller, J. Faaborg-Andersen: *Human placental lactogen and dU-estrogen levels in normal twin pregnancies*, Acta Genet Med Gemellol (Roma) 34 (1985) (1–2), pp. 59–65; R.L. TambyRaja, S.S. Ratnam: *Plasma steroid changes in twin pregnancies*, Prog Clin Biol Res 69A (1981), pp. 189–195; N. Ikeno and K. Takahashi: *Studies on changes in serum estrone, estradiol, estriol, DHA-S, and cortisol and urinary estriol excretion*, Nippon Sanka Fujinka Gakkai Zasshi 37 (1985) (1), pp. 99–106. See also on Estrogen levels in women with preeclampsia*:* W. Goldkrand: *Unconjugated estriol and cortisol in maternal and cord serum and amniotic fluid in normal and abnormal pregnancy*, Obstet Gynecol 52 (1978) (3), pp. 264–271; P.A. Long, D.A. Abell, N.A. Beischer: *Fetal growth and placental function assessed by urinary estriol excretion before the onset of pre-eclampsia*, Am J Obstet Gynecol 135 (1979) (3), pp. 344–347; A. Shibata, A.Y. Minn. *Perinatal sex hormones and risk of breast and prostate cancers in adulthood*, Epidemiol Rev 22 (2000) (2), pp. 239–248; On breast cancer see: Petersen, O.W., Gudjonsson, T., Villadsen, R., Bissell, M.J., and Ronnov-Jessen, L: *Epithelial progenitor cell lines as models of normal breast morphogenesis and neoplasia*. Cell Proliferation 36**,** Suppl. 33-44 (2003).

137. In para. 76 the US discusses the "Testicular dysgenesis syndrome" (TDS), which describes a HUMAN syndrome that is observed in the clinic! The relationship to animal studies is only made as an attempt to extrapolate possible reasons for the syndrome. In general, animal studies are designed to show effects in a small number of animals and, therefore, large doses are used in order to get effects in essentially all the exposed animals. However, it is a different situation for the human population where TDS-like symptoms are observed in a relatively small percentage of men. Thus, when genetic variation is taken into consideration, low-dose exposure of hundreds of millions of humans may in a small percentage of the exposed people lead to effects similar to those observed at high doses in all the animals in a small group of exposed animals. Moreover, humans are exposed to a mixture of compounds and it has been shown that the effects represent the sum of all the different exposures (i.e. concentration addition!).

138. In para. 77 the US dismisses the effects of DBP because it "is a well known reproductive toxicant". However, DBP in an endocrine disrupter and acts by reducing the testosterone production in the Leydig cells of the testes and thereby DBP is an example of a compound that induces TDS-like symptoms via effects on the endocrine system, by lowering the testosterone levels.

139. Unlike the US comments in paras. 79 and 81, it seems clear that Dr. Sippell's conclusion "exposure during pregnancy might result in severe transplacental virilisation of a female fetus" is reasonable, since it has been shown that trenbolone is about 3 times more potent that testosterone and

given that trenbolone is extensively used as an androgen by body builders. This strongly suggests that trenbolone is a potent androgen in humans.

140. Despite the US comments in para. 80, there are now several studies on the estrogenic potency of Zeranol (e.g. Guevel & Pakdel 2001; Liu & Lin, 2004) and all essentially report the same potency (which is similar to that of estradiol). The *Leffers et al* paper analysed the induction of several estrogen-regulated genes and found that different genes responded differently to the tested estrogens. However, the *Leffers et al.* paper did not measure cell proliferation and none of the analysed genes were proliferation-sensitive. The observation that DES and estradiol (and Zeranol) were equipotent depended on which genes were used for the analysis. The key finding in the *Leffers et al*. paper, which the US apparently fails or does not wish to accept, is that Zeranol is as potent as estradiol and that has now been confirmed by other studies. See in particular: Le Guevel R, Pakdel F: *Assessment of oestrogenic potency of chemicals used as growth promoter by in-vitro methods*, in Hum Reprod. 2001 16,1030-1036 (Exhibit EC – 108); and Liu S, Lin YC: *Transformation of MCF-10A human breast epithelial cells by zeranol and estradiol-17beta*, in Breast J. 2004 10, 514-521 (Exhibit EC – 62).

Canada's comment

141. Contrary to what Canada asserts, Dr. Boisseau is not criticizing the "excess exposure" but merely asks for its assessment and comparison. In other words, by its reply Dr. Boisseau actually confirms that an "excess exposure" exists.

142. In its comments on Dr. Sippell's reply, Canada is making again an unqualified statement concerning the "controversial" bioassay methodology. However, Canada does not offer any supporting arguments for its blunt statement. Furthermore, Canada pretends that "the experts have contested" elsewhere the conclusions of the European Communities' quote. This is not true. Canada would be well advised to respect more accurately the various experts' replies instead of using an unqualified and misleading language in order to manipulate the Panel.

Q40. The European Communities states that "the levels of endogenous production of the hormones by prepubertal children is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship..." Please comment on the methodology used by the SCVPH to support the conclusion that hormone levels are lower than previously thought, and in particular comment on the validity of these methodologies and their conclusions. Would your conclusions have been the same at the time of adoption of the Directive in September 2003?

US comment

143. The United States refers to Dr. Boobis' reply to this question in paragraphs 28, 65 through 67 and 83 of its submission. There is a discussion of Dr. Sippell's view on assay validation in paragraph 66 of the submission, on which the European Communities has already commented above.

Canada's comment

144. Canada refers to the "concerns" by Dr. Boisseau as expressed in its reply to Question 38. However, as already mentioned above, Canada is not accurately interpreting Dr. Boisseau's reply and it abuses the expert's response to pursue its own litigation objective. In the same vein, it is quite superficial when Canada, in paragraph 150, refers to "concerns highlighted by the experts about the SCVPH's use of this methodology". If at all, there is only one expert, Dr. Boobis who makes some critical remarks, while Dr. Boisseau remains neutral, Dr. Sippell supports the methodology and Dr. Guttenplan, Dr. Cogliano and Dr. De Brabander do not express themselves at this stage. Even

more, Dr. Guttenplan, in his response to Question 52 states that: "[a]lthough the US and Canada question the accuracy of the assay originally employed for estrogens at the low levels found in children, recent reports (…) indicate more recently reported levels used by the EC are accurate".

145. Concerning the in vitro assay developed independently by Klein *et al* and F Paris *et al* to assay low amounts of receptor-active estrogens, it should be added to what has been explained above that these biological assays are not absolute in the sense that they should give precise and absolute values. Indeed, they are internally validated assays but not yet inter-laboratory comparison has been made. But even if one may consider that this is a drawback, the assay is very useful in that it is far more sensitive than any other spectro-physical assay based on mass spectrometry. Nevertheless, this inter-technique comparison will be performed rather soon thanks to the new generation of mass spectrometry based on Fourier-Transformed MS. This technological progress should be useful to perform the complete hormonal exploration (androgens, estrogens) in plasma of no- and pre-pubertal girls and boys and the results will be critical to the risk assessment exercise. Conversely, the JECFA evaluation was based on old and very questionable data that were not produced at that time by any spectro-physical method but only by radio-immunologic assays.

Q41. Why would individuals with the lowest endogenous hormone levels be at greatest risk? How would the risks for these individuals arising from hormones naturally present in meat differ from the risks arising from the residues of hormone growth promoters?

US comment

146. The United States does not dispute the experts' (Drs. Boisseau, Sippell) replies to this question, which confirm the view taken by the European Communities that prepubertal children are particularly sensitive to hormones exposure.

Canada's comment

147. As in its comments on earlier question, Canada claims support by "the experts" for the criticism on the Klein assay which, however, is not supported by the facts. Thus, Canada's criticism on the detailed reply by Dr. Sippell is completely baseless.

Q42. To what extent, in your view, has JECFA taken into account the particular situation of sensitive populations, in particular prepubertal children, in its risk assessments with respect to oestradiol-17β? Please compare the original data concerning endogenous production of natural hormones by prepubertal children upon which JECFA based its assessment and those used by the European Communities in its risk assessment. In your view, does the scientific material referred to by the European Communities require a revision of the Codex recommendation with respect to oestradiol-17β? [For the questions in this section, see paras. 121-122 of EC Rebuttal Submission (US case), para. 103-104 of EC Rebuttal Submission (Canada case), Exhibits EC-88, 99, paras. 42-45 of US Rebuttal Submission, paras. 84 and 159 of US First Submission, and for JECFA's work Exhibits CDA-11, 16, 17, 18, 39]

US and Canada's comments

148. The United States refers to Dr. Boobis' and Sippell' replies to this question in paragraphs 67, 84 and 85 of its submission (no reference to Dr. Boisseau). In Footnote 178 of its submission, the United States dismisses Dr. Sippell's view that JECFA has not adequately taken into account the particular situation of sensitive populations, in particular infants and prepubertal children. The United States claims that it is unclear whether Dr. Sippell is familiar with JECFA's safety factors or whether/why he finds these factors to be inadequate. However, none of the US comments is valid because the so-called safety factors cannot substitute for the need of JECFA to review these hormones

on the basis of the most recent scientific data, including in particular the direct genotoxicity and the low levels of endogenous production by prepubertal children.

149. Similarly, Canada fails to address Dr. Sippell's detailed and supported criticism of the JECFA conclusions. The European Communities regrets Canada's selective perception of all experts' replies and to respond adequately to criticism on the use of hormones as growth promoters.

(e) Bioavailability

Q43. Please define bioavailability, comment on the significance of bioavailability to assessments of risk, and on the degree of bioavailabilitiy of the residues of the hormones at issue when consumed in meat, taking into account parties' differing views on this matter. [see paras. 123-124 of EC Rebuttal Submission (US case), paras. 105-106 of EC Rebuttal Submission (Canada case), paras. 100, 155-159 of the EC Replies to Panel Questions, paras. 32 and 41-42 of US Rebuttal Submission, paras. 69, 71, 88-89 and 146 of US First Submission, and para. 134 of Canada Rebuttal Submission]

US comment

150. The United States claims that "none of the experts' responses appear to indicate otherwise", when claiming that the European Communities has failed to take into account the low bioavailability of estradiol 17β in its assessment of that hormones (see paragraph 27 of its submission). This is plainly wrong as Dr. Guttenplan comes to the opposite conclusion when stating that: "[i]t appears that the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account. (Estrone is readily inter-convertible with estrogen). Calculations are presented in the above reference that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children (EC Rebut, para. 122). This would represent a risk factor (EC Rebut, para. 122)."

151. Indeed, the United States tries to refute the view taken by Dr. Guttenplan by arguing that (1) he relies on materials cited by the European Communities that do not in fact demonstrate a higher bioavailability for estradiol 17β than previously thought, and (2) he miscasts as "paradoxical" a US argument relating to bioavailability (paragraphs 28 and following of the US submission).

152. As for the first argument, it should be recalled that human beings are considered as having a monogastric physiology and, consequently, the large digestibility of nutrients should be clearly applicable. Therefore, for risk assessment purposes it is considered that digestibility and hence bioavailability of steroids ("primary bioavailability" or the amount of xenobiotics absorbed from a given matrix or formulation) and in particularly estrogens is more or less complete. In the absence of any specific study on bioavailability of steroids considering the low amounts of residues found in edible tissues of treated cattle, there is a need to consider this bioavailability parameter at its maximal value due to a complete intestinal absorption. This point has been formerly anticipated in milk-fed calves which have kept a seemingly monogastric physiology and for which the estrogens excretion is mainly achieved by urinary route, that is strikingly different from this obtained for ruminant physiology, which prove the important entero-hepatic cycle and hence the very significant intestinal absorption of estrogens. This also explains the bioavailability of hormones present in gut, even if they are excreted by the biliary route. In addition, there is a need of common understanding of what is the definition of bioavailability of steroidal hormones, given the greatly varying degrees between gut, liver and peripheral tissues, due to the progressive metabolism of those hormones. Again, we need to consider that there is total intestinal absorption and a complete hormonal effect at least on intestinal cells and hepatocytes before their metabolic degradation. Therefore, it is very doubtful when JECFA and Dr. Boobis assume that an oral bioavailability of rate of 5% (Fortherby, 1996) is rightly used in

order to assert there is a low hormonal effect of orally given hormones. This result may be only a comparative result of hormonal effect of two different administration routes on classically considered target tissues and is related to raw bioequivalence measured on a given target tissue, not the bioavailability. In the context of hormone residues in meat, no specific results have been obtained on the hormonal response of intestinal cells exposed to those hormonal residues neither on hepatic cells measurements have been carried.

153. Some specific attention should also be placed on the different bioavailability rates of estrogens, considering that some are ingested as free or conjugates compounds (thus being easily hydrolyzed by gut microflora) and some other are lipophilic compounds (estrogen esters) and are susceptible to take the lymph route after intestinal absorption (see Paris et al, 2000). Therefore, this class of lipoidal estrogenic residues will partially escape the liver degradation step. This specific bioavalability of estrogen esters may explain why, even by oral route administration, they are about 10 fold more active than estradiol in inducing a significant uterotrophic response in the juvenile female rat model (Paris et al, APMIS 109 (2001) 365-375) (Exhibit EC-117). This has been taken into account by the SCVPH, unlike JECFA and Dr. Boobis that seem to disregard it.

Canada's comment

154. Canada fails to address specifically the conclusion by Dr. Guttenplan whereby "calculations are presented in the above reference that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children (EC Rebut, para. 122). This would represent a risk factor (EC Rebut, para. 122)".

(f) Good veterinary practice (GVP)

Q44. Please define "good veterinary practice" (GVP) and/or "good practice in the use of veterinary drugs" (GPVD). What are the relevant Codex standards, guidelines or recommendations relating to GVP/GPVD? Please comment on the statement by the European Communities that the definition of the GPVD is "circular and hence problematic." [see para. 88 of the EC Replies to Panel Questions]

US comment

155. The United States does not comment on this point and the replies given by Dr. De Brabander and Dr. Boisseau (on the discussion in paragraph 107 of its submission see below, question 45).

Canada's comment

156. Canada, regrettably, does not address Dr. De Brabander's reply on why the definition of the GPVD is considered to be "somewhat circular and hence problematic". Instead, Canada just reproduces a general statement by Dr. Boisseau although even Dr. Boisseau provides an interpretation which Canada, again, ignores.

Q45. In conducting a risk assessment of specific veterinary drugs, what assumptions are made concerning GVP, if any? How, if at all, are risks that might arise from the failure to follow good veterinary practice in the administration of veterinary drugs addressed?

US comment

157. In the context of this question the United States comments on the reply given by Dr. De Brabander in paragraph 107 of its submission dismissing the reference he makes to evidence

of abuse of hormonal substances in the US. While the study referred to by Dr. De Brabander is certainly interesting, the European Communities would recall that it has undertaken its own studies to assess the possibility of misuse and abuse in the US and Canada. It is on these studies that the EC risk assessment relies on.

Canada's comment

158. Canada does not comment on Dr. De Brabander's pertinent response whereby "farmers (and vets) have indeed economic incentives to misuse growth promotion substance (implants or others)". The Panel may draw its own conclusion by this Canadian failure.

Q46. To what extent were risks from misuse or abuse assessed by JECFA in its evaluation of the hormones at issue? In terms of the three synthetic hormones at issue, how is GVP relevant to the establishment of MRLs by JECFA?

US and Canada's comments

159. The United States and Canada does not refer to or discuss in detail the experts' (Drs. De Brabander, Boisseau, Boobis) replies to this question.

Q47. How significant are any differences in GVP in the European Communities, the United States, and Canada? Does the EC risk assessment take into account relevant control mechanisms with respect to GVP in place in the United States and/or Canada? If so, what are their conclusions?

US and Canada's comments

160. The comments above under Question 45 apply here as well. In addition, Canada argues (at para. 182) that the comment of Dr. De Brabander that control mechanisms short of total ban is "deeply flawed". However, Canada - as well as the US – fails to discuss at all the numerous instances of abuse and misuse documented in the EC inspections in their territories, nor do they comment on the findings of the evidence reported in exhibits EC-67 to 73.

Q48. To what extent does the scientific evidence referred to by the European Communities assess risks to human health from residues of misplaced implants or improper administration, i.e. when administered differently than indicated on the label of the manufacturer or contrary to GVP, of any of the six hormones? Would your reply have been different at the time of adoption of the EC Directive in September 2003? What are the potential hazards, if any, to human health of the use of large quantities, or doses higher than recommended, of any of the six hormones in dispute?

US comment

161. The United States refers to the experts' (Drs. Boobis, De Brabander, Boisseau) replies to this question in paragraphs 103, 104 and 109 of its submission. As stated in its own comments, the conclusions reached by Drs. Boisseau and Boobis rest on the assumption that a quantitative assessment is required. Indeed, Dr. Boobis concedes that this is not the view taken by the EC risk assessors, a remark which the United States conveniently omits to refer to or comment on. The US criticises the statements by Dr. De Brabander as not based on evidence, but as explained above in relation to Question 47 the evidence is provided in the relevant EC exhibits which the US has chosen to ignore.

Canada's comment

162. The way Canada comments on the three expert replies is again an interesting and typical example on how Canada attempts to influence the Panel by a selective reproduction of only those expert replies which, in Canada's view', supports its position. However, instead of looking for comfort in replies that merely allegedly confirm its own position (which is a natural and convenient way of doing but insufficient in this case) Canada should have better addressed Dr. De Brabander's very critical conclusion whereby "more and more scientific data sustain the ban on the use of hormones: the economical profits resulting from using hormones does not balance the potential danger [in respect of, *inter alia*, animal welfare, environment and transformation of hormones] **in all of its aspects**" (emphasis in the original).

Q49. What analytical methods, or other technical means, for residue detection in tissues exist to control the use of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice? What tools are available to control the use by farmers of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice?

US comment

163. The United States does not refer to or discuss Dr. De Brabander's reply to this question. Moreover, as the European Communities has explained, these hormones are dispensed over the counter (OTC) in the US and Canada. In such a case the concept of GVP is not applicable and can be even misleading. Veterinarians are not involved in the whole process of distribution and administration of these hormones to animals since any farmer is free to use them at his will. Therefore, the initial statement by Dr. Boobis that "… it has been used as an anabolic agent in veterinary practice" is totally misleading as regards the realistic conditions of use of these hormones in the US and Canada. Moreover, the pinna of the ear is the only authorized site of application.[9] If this is not observed, the depot goes directly into the edible part of the animal. Thus, it is more than surprising that this issue of utmost importance is not covered by any reply from the defending parties and the experts. Dr. Boisseau states that the administration of the implant is "… by subcutaneous implant to the base of the ear …". If this is so, this is already a serious misuse of these implants.

Canada's comment

164. The European Communities agrees that the additional information asked by Canada may be asked from Dr. De Brabander. The European Communities is confident that this also will support its position.

Q50. Are there other measures available to the European Communities (other than a complete ban) which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

[9] See in the US the freedom of information summary, supplemental new animal drug application, NADA 140-897; Route of Administration: Subcutaneous implantation on the posterior aspect of the middle one-third of the ear by means of an implant gun; and freedom of information summary, supplemental new animal drug application, NADA 140-897, the Center for Veterinary Medicine has concluded that, for these products, adequate directions for use by layperson have been provided and the products will have over-the-counter (OTC) status. Label directions are accompanied by pictorial diagrams and detailed instruction in plain language. The drugs are not controlled substances. The products' status remains OTC. The labelling is adequate for the intended use and has sufficient warnings/statements to prevent illegal use in veal calves.

US comment

165. The United States does not refer to or comment on Dr. De Brabander's reply to this question, which is entirely supportive of the position taken by the European Communities.

Canada's comment

166. In its comments on Dr. De Brabander's reply Canada fails to see the difference between, on the one hand, the theoretical possibilities of control possibilities, as provided by Dr. De Brabander in his reply to Question 49, and the actual possibility to address risks arising from misuse and the failure to follow GVP and which, in Dr. De Brabander's view, can only be achieved by the European Communities through a complete ban. There is no contradiction between these two statements.

Q51. Does the material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada call into question the potential applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada? [For questions on GVP see the SCVPH Opinions in Exhibits US-1, 4 and 17, paras. 125-127 of EC Rebuttal Submission (US case), paras. 107-109 of EC Rebuttal Submission (Canada case), para. 154 of EC Replies to Panel Questions, Exhibits EC-12, 67, 68, 69, 70, 73, 96, 102, 103, paras. 32 and 54-65 of US Rebuttal Submission, para. 75 of US First Submission, paras. 107-111 of Canada Rebuttal Submission, page 40 of Exhibit CDA-27]

US comment

167. The United States refers to Dr. Boisseau's reply in paragraph 108 and comments on Dr. De Brabander's reply in paragraph 111 of its submission. The US relies again on the statements by Dr. Boobis (in paras. 109-110) to counter the evidence on abuse and misuse produced by the European Communities. But neither Dr. Boobis nor the US contest as such the accuracy of the scientific findings reported in those studies. Dr. Boobis' only claim is that (at para. 109) that the "probability" of these happening is "extremely low". However, what is "extremely low" is not defined nor is it true of course.

Canada's comment

168. Canada draws the conclusion from Dr. Boisseau's reply that "in the unlikely event that GVP is not followed, the applicability of Codex standards is not put into doubt". However, Dr. Boisseau never said this. Rather, Dr. Boisseau explicitly agreed that "the European Communities is right to state that, in case of these different misuses/abuses, the exposure of consumers may be totally different" (Dr. Boisseau's reply to Question 48).

(g) Other

Q52. Do the risk assessment of the European Communities or any other scientific materials referred to by the European Communities demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes? If yes, why? If not, what kind of evidence would be required to demonstrate such potential adverse affects? Would your response have been different at the time of adoption of the Directive in September 2003?

US comment

169. Apart from a wholesale reference to Dr. Boobis' reply in footnote 41, the United States does neither refer to nor discuss the experts' (Drs. Boobis, Boisseau, Guttenplan) replies to this question.

Canada's comment

170. Canada attempts again to mislead the Panel by drawing conclusions that are not warranted, in particular when it misstates (at paras. 197-198) the reply of Dr. Guttenplan. If to the reply by Dr. Guttenplan are added the replies from the other 3 scientists who replied in their areas of expertise, then 4 out of the 6 scientists, in the view of the European Communities, agree with its scientific basis and the risk assessment it has conducted on these hormones. The European Communities would suggest that the Panel requests each of the experts to respond to this question for his respective areas of expertise.

Q53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations? Would the systematic use of these and the synthetic hormones in combination have any implications on how the scientific experiments and the risk assessments are to be carried out? If so, have the scientific materials referred to by the European Communities or relevant JECFA reports taken into account the possible synergistic effects of such combinations on human health? [see sections 4.2-4.3 of the Opinion of the SCVPH of 2002 in US Exhibit 1]

US comment

171. The United States does neither refer to nor comment on the experts' (Drs. Boisseau, Guttenplan) replies to this question.

Canada's comment

172. Canada's statement is, to say the least confusing. First, Canada pretends that Dr. Boisseau and Dr. Guttenplan "advise that the exposure to these hormones, both alone and in combination is so low that there is very little risk of any increase in the risk if assessed in combination". Yet, this description falls short by what Dr. Boisseau or Dr. Guttenplan actually stated. Dr. Boisseau merely states that "[c]onsidering that it has been established that progesterone and testosterone are not genotoxic, it is not likely that the testing of combinations of progesterone and testosterone with oestradiol-17β would have led to synergistic effects compared with those obtained from these individual substances". Dr. Guttenplan, for his part, states that "the use of mixtures should complicate risk assessment/scientific experiments, as they would have to evaluate/investigate each component alone and in combination. This is a major undertaking as effects of individual agents may be additive, inhibitory, and synergistic or there may no effect. It appears from the evidence submitted that, by far, estrogen is the major agent of risk and because the concentrations of all of the hormones in beef are so low, that they would be unlikely to affect the potency of estrogen. However, it appears that no experiments on effects of combinations were performed, so some uncertainty exists here".

173. Against this background, Canada's conclusion that "once oestradiol 17β has been demonstrated not to have effects when used as a growth promoter, there is little risk that adverse effects would occur if used in combination with the other hormones" has never been stated by any of the experts.

Q54. What is the acceptable level of risk reflected in the Codex standards for the five hormones at issue? How does this compare to the European Communities' stated objective of

"no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion". [see para. 149 of EC Rebuttal Submission (US case)]

US comment

174. The United States does neither refer to nor comment on the experts' (Drs. Boisseau, Boobis, Guttenplan) replies to this question.

Canada's comment

175. The comments by Canada about "theoretical" and "real" risk are again misleading, because the scientists (Drs. Guttenplan, De Brabander and Sippell) and the European Communities have identified a real risk from the consumption of residues in meat from animals treated with these hormones for growth promotion purposes. The existence of the real risk has been confirmed also by the US 2002 Carcinogenesis Report and it is simply a question of defining the appropriate level of protection – which is much lower in the US and Canada than in the European Communities – that has so far led the defending parties from ignoring the regulatory implications of that finding. This is not different from what has happened in the case of Carbadox a few years ago, when the defending parties were arguing this case in 1997 before the WTO. It is useful to recall here how Canada has explained its 360 turn on Carbadox in 2000, just 3 years after its persistent insistence in the WTO that Carbadox was a safe substance to use:

> "Carbadox is an antibiotic approved in the 1970s for use in swine to prevent and treat disease as well as to maintain weight gain during periods of stress, such as weaning. It has been shown that the drug, and the by-products of the drug that occur when the drug is metabolized in the body, can cause cancer in rats. However, when an appropriate withdrawal period (i.e stopping the administration of the drug before slaughter) is observed, the drug and its breakdown products are not found in the food derived from the treated animal. Carbadox was approved on the basis that this specified 35-day withdrawal period be strictly observed.
>
> However**, reports of misuse and accidental contamination**, combined with **a better scientific capacity** to detect breakdown products of carbadox, resulted in serious concerns about the safety of the product. The first reported incident occurred in the fall of 2000 when pigs at a farm in Quebec were accidentally fed carbadox and slaughtered without respecting the withdrawal period. All affected product was recalled and removed from store shelves and an investigation into the incident was launched. The investigation was then broadened to review the use of carbadox throughout the Canadian pork industry.
>
> In February 2001, responding to the European Union Fall 2000 audit of the Canadian Program for the Control of Residues, Canada made a public commitment to reassess the use of carbadox in pigs.
>
> Based on the reassessment, Health Canada proposed to amend the Food and Drug Regulations to ban the sale of any drug containing carbadox for administration to food-producing animals."[10] (Emphasis added)

Q55. Do the Opinions of the European Communities or other scientific materials referred to by the European Communities evaluate the extent to which residues of growth promoting

[10] See at the website of Health Canada at: http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2001/2001_88_e.html, visited on 11 July 2006.

hormones in meat contribute to what the European Communities calls "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings"? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 151 of EC Replies to Panel Questions, paras. 43-44 of US Rebuttal Submission, paras. 83-85 of Canada's Rebuttal Submission]

US and Canada's comments

176. The United States refers to Dr. Boisseau's and Dr. Guttenplan's replies in paragraphs 23 and 25 of its submission but fails to put in doubt the accuracy of Dr. Guttenplan's comments. The fact is that the decision of JECFA to set an ADI for oestradiol 17β was based on the alleged lack of evidence for *in vivo* genotoxicity and the seemingly safe use of oral contraceptives and postmenopausal estrogen replacements, implying the existence of a threshold for the carcinogenic effect of oestradiol 17β. But both situations are wrong and in any case have changed in the meantime, as there is now clear evidence for *in vivo* genotoxicity and evidence for an increased risk of cancer in women taking oral contraceptives and postmenopausal estrogen therapy. Even if a threshold would exist (which should not because of genotoxicity), the endogenous production of oestradiol 17β obviously exceeds that threshold, because we see oestrogen mediated cancer of the breast, endometrium and ovary in women. So any additional exposure to estrogens, e.g. from food, will inevitably increase the risk.

177. Moreover, as the EC has explained above, the US criticism that the EC statement "any excess exposure would increase the risk" is incorrect because the concept of concentration additivity has been proven for estrogens, including the demonstration of "0+0 ≈ 0" (i.e. that two doses which alone do not produce any detectable effects, when added together result in an observable effect). Thus, it is clear that any dose matters.

Q56. Has JECFA/Codex considered in its risk assessment of the five hormones such "additive risks? Are there internationally recognized guidelines for conducting assessments of "additive risks"?

US comment

178. The European Communities suggests that it be clarified at the hearing where in its assessment JECFA is considering the issue of additive risks. United States refers to Drs. Boisseau's and Boobis' reply to this question in paragraph 26 of its submission, but again uses the idea of "trivial increase, something it is obviously unable to prove with scientific evidence. Indeed, quite the opposite is true. It has been shown that additivity of an exogenous dose to an endogenous hormone that is already causing responses will increase risk and have no threshold (see Hoel, D.G., Incorporation of background in dose-response models, in Fed. Proc. 39, 73-75 (1980)). Nonetheless, non-linearity (a threshold) is assumed.

Canada's comment

179. Canada's comments on the expert' replies only tell half of the story. Indeed, Canada fails to see that Dr. Boisseau stated that for the synthetic hormonal growth promoters, JECFA/CODEX did not consider such "additive risks" probably because no internationally recognized guidelines for conducting assessment of "additive risks" exists. Canada's comment cites with approval Dr. Boobis reply. But the "additive" risk they both have in mind is quite different from the additive risk the European Communities has explained. For both of them, JECFA is supposed to take into account such risks through the mechanism of "safety margins" and default assumptions, which are obviously totally inadequate and scientifically inappropriate for this type of genotoxic substances.

Q57. Canada comments that "one single molecule that the European Communities considers so dangerous from meat derived from animals treated with hormone growth promoters is suddenly not at all that dangerous when consumed from meat from animals treated for therapeutic or zootechnical purposes. The European Communities' concern about the genotoxic potential of oestradiol-17β suddenly and inexplicably disappears." To what extent are hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes, taken into account by the European Communities, if at all, in its assessment of the cumulative effects from the consumption of meat containing residues of the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 97 of Canada Rebuttal Submission; paras. 17-20 of US Opening Statement]

US comment

180. The United States refers to the experts' (Drs. Boisseau, Boobis, Guttenplan) replies to this question in paragraph 24 of its submission. Contrary to what the United States claims, Dr. Guttenplan does address the Panel's inquiry, i.e. whether the European Communities, in its Opinions, took these treatments into account in an assessment of cumulative effects. He states that the European Communities "does not really take [these] […] into account in their risk assessment." Dr. Guttenplan then refers to the reasons why this is so and qualifies these as "a reasonable response."

Canada's comment

181. Canada draws the wrong conclusion from the expert's reply when it purports that "the experts' advice indicates that the EC is trying to have it both ways: that hormones are genotoxic for some purposes and not others". Indeed, while Dr. Boisseau is questioning the logic of the EC's limited exception for the use of hormones for zootechnical and therapeutic reasons, Dr. Guttenplan expressly states its support for the EC' approach. This is not a question about the genotoxicity of hormones, as Canada tries to present it, but it is a pure risk management decision whereby in these limited circumstances it is assumed that the hormones will not enter into the food chain and, therefore, logically not present a risk to consumer's health. For this reason, it is by the way also an incorrect conclusion by Dr. Boisseau that this limited exception would raise questions regarding the overall approach taken by the European Communities. Indeed, the European Communities has always been pursuing the objective of health protection. This objective is not put into danger in case of the use of these hormones for zootechnical and therapeutic reasons, which in any case has been rejected by the Appellate Body back in 1998.

Q58. Please comment on the EC statement in para. 94 of the EC Replies to Panel Questions that "the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be", taking into account para. 105 of Canada Rebuttal Submission.

US comment

182. The United States refers to the experts' (Drs. Boobis, Guttenplan, Boisseau) replies to this question in paragraphs 24 and 25 of its submission. Quoting Dr. Guttenplan as referring to an "indeed very weak statement of the EC", it conveniently omits the rest of Dr. Guttenplan's statement who went on to say "[h]owever, the alternative would be to suggest a risk that might be wildly inaccurate, due to the limitations imposed by the lack of solid data on levels of hormones in meat. Perhaps a better approach would have been to suggest several scenarios. These could be validated or disproved by subsequent studies." Thus, Dr. Guttenplan suggests that other alternative scenarios. The European Communities considers that the Panel may request Dr. Guttenplan to explain what other scenarios he has had in mind.

Canada's comment

183. The comment by Canada (at para. 210) is also incomplete and partly false, because the European Communities has demonstrated that if the appropriate levels of endogenous production are taken into account, the ADIs set by JECFA will be reached and will be even exceeded easily.

Q59. Does the scientific evidence referred to by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see para. 132 of Canada Rebuttal Submission]

US and Canada's comments

184. The United States refers to the experts' (Drs. Boobis, Boisseau and Guttenplan) replies to this question in paragraph 86 of its submission. Canada discuss this in para. 211 of its submission. They both do not comment on the fact that there is a straightforward contradiction in the statements they quote. While Dr. Boobis denies that there is any evidence of adverse effect on the immune system, both Dr. Boisseau and Dr. Guttenplan acknowledge that there is such evidence.

Q60. Does the scientific evidence referred to by the European Communities identify and evaluate whether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives (MGA) or implanted? Are you aware of any differences?

US comment

185. The United States only refers to Dr. Guttenplan's reply to this question. In footnote 114 of its submission it states that Dr. Guttenplan's statement that MGA can be administered both as feed additive or implant is incorrect.

Canada's comment

186. Canada's claim (at para. 212) that Dr. Boobis is right in arguing that misuse would "not occur in feed additives" is without any basis. The example of Carbadox may be again useful, because this substance too was administered as a feed additive. But as the European Communities has explained above in relation to Question 54, Canada has admitted that its misuse has occurred and actually to such an extent as to lead it to ban this product also on this ground

Q61. In your view and in the light of information provided by the parties as well as the work undertaken at JECFA and Codex, did the scientific evidence available to the European Communities at the time it adopted its Directive (September 2003) allow it to conduct an assessment (quantitatively or qualitatively) of the potential for adverse effects on human health arising from the consumption of meat from cattle treated with (a) progesterone; (b) testosterone; (c) trenbolone; (d) zeranol; and (e) melengestrol acetate? Would your response differ in light of the scientific evidence provided which is subsequent to the adoption of the EC Directive?

US and Canada's comments

187. As so often, the United States' claim that "*the* experts' responses confirm that the scientific evidence and information relating to the five hormones is sufficient to conduct an assessment" does

not reflect the reality of what the experts have said. Indeed, only Dr. Boobis has taken this view (paragraphs 48 and 49 of its submission).

188. Dr. Boisseau declines to comment on the question itself noting that "I don't really know what were the data available to the European Communities at the time it adopted its directive." Furthermore, Dr. Guttenplan takes a very nuanced and partly opposite view. As regards Trenbolone and Zeranol, he states that from the data available at the time of the Directive, the potential for adverse effects could not be ruled out. The United States tries to undermine this statement by pointing out that Dr. Guttenplan mistakenly thinks that trenbolone is an estrogen.

189. However, Dr. Guttenplan may not be wrong completely as *Bauer et al.* have documented that trenbolone has three separate hormonal activities combined in one substance. It binds to the androgen receptor, progestin receptor and glucocorticoid receptor. This was not documented before. Dr. Boobis and certainly the US (at para. 49) in their statements still call trenbolene an androgen. The finding above is of clear relevance for the risk assessment of trenbolone acetate. If multiple hormonal activities are exhibited from one and the same compound, the potential of the synergistic activity has to be considered. See Bauer ERS., Daxenberger A., Petri T., Sauerwein H. and Meyer HHD.: *Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and to the bovine progestin receptor,* in APMIS 108: 838-846, (2000)(Exhibit EC – 15).

190. The European Communities would disagree however with the statement by Dr. Guttenplan that the evidence for MGA and its assessment "seems sound" and would like that the Panel requests Dr. Guttenplan to provide a more detailed explanation of his statement on this point, taking into account in particular the new evidence produced by the European Communities.

191. The European Communities considers that also the other experts who have not expressed an opinion on this question should be requested by the Panel to take a position in their own areas of expertise, since it seems to the European Communities – from their replies to the other questions – that in their view the evidence available did not allow the European Communities to conduct a full and complete risk assessment.

Q62. Does the scientific evidence relied upon by the European Communities support the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [Please see the following references for the two questions above:

- **paras. 58-94 and 125-129 of US First Submission, paras. 28-32 of US Rebuttal Submission**
- **paras. 116-124 of Canada First Submission, paras. 74, 130-135 of Canada Rebuttal Submission (Exhibit CDA-23)**
- **paras. 108, 147, 162-169 of EC Replies to Panel Questions, paras. 143-174 of EC Rebuttal Submission (US case), and paras. 148-166 of EC Rebuttal Submission (Canada case)**
- **Exhibit CDA-32 provides a detailed table outlining the chronology of JECFA's assessment of these hormones and the resulting documentation]**

US and Canada's comments

192. The United States refers to the experts' (Drs. Boisseau, Boobis and Guttenplan) replies to this question in paragraphs 49 through 53, 90, 103, 109 and 110. As so often, it pretends that "*the* experts' replies" confirm its view where only one or two have done so and another one has taken the opposite view (paragraphs 51 and following). Indeed Dr. Guttenplan has listed a number of examples where the 17 studies have identified important gaps. The United States claims that the majority of those relate to oestradiol 17β and therefore are not relevant for the purposes of the provisional an on the other five hormonal substances (paragraph 52). This allegation is erroneous.

193. In particular, it is again useful to review some of the comments provided by Dr. Boobis for each of the studies funded by the European Communities in order to determine their relevance and the gaps and level of uncertainty they have established.

194. Concerning the study "re: experimental studies in rabbits by Rajpert-De Meyts et al.", only a part of the study concerning metabolism and placental transfer has been published so far (Lange et al. Xenobiotica 2002). The results on the reproductive effects of Zeranol (ZER), Trenbolone Acetate (TBA) and Melengestrol Acetate (MGA) in rabbits exposed during development were summarized in a detailed report (by Rajpert-De Meyts et al.) sent to the European Communities in December 2001 with additional data supplemented in the spring 2002. The study has not yet been submitted for publication elsewhere for the following reasons:

- similar findings concerning the effects of ZER and Estradiol on spermatogenesis and epididymal reserves were previously published in another animal model (bull) by Veeramachaneni et al. Environ & Appl Toxicol 1988; 10: 73-81, thus this part of the rabbit study was only confirmatory;

- in the course of the rabbit study, hundreds of samples of tissues, sera and semen were collected and stored, and only a part of investigations have been completed due to lacking funds. Some ensuing studies are still in progress. The study will be submitted for publication when these investigations have been finalized.

195. The evaluation of the *Lange et al.* study and the report (Rajpert-De Meyts et al.) by Dr. Boobis is one-sided. The sentence stating that *"there was no net accumulation of the compounds in fetal tissues"* is only partially true. The concentrations of the residues after MGA treatment were in fact higher in the fetal muscle than in the maternal muscle, the fact not mentioned by him.

196. The unpublished part of the study of the exposure at three different developmental stages provided a wealth of data, which are dismissed by Dr. Boobis with a following statement: *"It is not clear whether the changes observed were consistent and hence compound-related as only a single dose was used for each compound* ". The report did, in fact, very clearly state that the study was preceded by a dose-finding pilot study that investigated three different doses of all three compounds. Because the higher doses caused extensive adverse changes, only the lowest doses were selected for the definitive study. Contrary to Dr. Boobis' statement - *"nor is it apparent whether the magnitude of all changes discussed reached statistical significance*" - a detailed statistical analysis was performed, with all significant changes at $p<0.01$ and $p<0.05$, showing effects of the anabolic steroid used, clearly highlighted in the report.

197. Concerning the study "re: genotoxic potential of xenobiotic growth promoters and their metabolites", it is true that this study has not provided clear evidence for the genotoxicity of trenbolone, melengestrol acetate and zeranol in several in *vitro test* systems. However, the metabolism studies have clearly shown that all three compounds give rise to numerous hitherto unknown metabolites, which may or may not have adverse effects. Therefore, the value of this study is the

demonstration that the fate of all three xenobiotic growth promoters in the organism may be far more complex than previously thought. Unfortunately, none of the novel metabolites could be structurally elucidated in the limited time period of the study, which prevented publication in peer-reviewed journals. Nonetheless, the structures of these novel metabolites and their biological activities need to be further studied in order to improve the risk assessment. The same applies to the observation of DNA adduct formation, though at low level, of trenbolone in rat hepatocytes by the post-labeling assay. Whether these adducts contain trenbolone or not, they should be further characterized in order to make sure they do not pose a risk.

198. Concerning the set of studies "re: estradiol metabolism in cattle", Dr Boobis has well noticed the presence of estradiol-17-esters as tissular residues. Nevertheless, his comment does not integrate a possible different absorption route by the lymphatic circulation. This specific point has been demonstrated in the same set of studies in cannulated piglets. Concerning this specific class of estrogens, currently there is a gap in our knowledge of the extent to which they have some hormonal effect in peripheral tissue but also in intestine when ingested. Moreover, when considering the *in situ* catechol estrogens formation in target tissues of exposed consumers (in particular at the intestine level), there is still a gap about the complete residue information on the parent compound but also on the metabolites, specifically on estradiol-alpha. This latter compound gives the same DNA-adducts pattern from catechols as estradiol (Jouanin *et al*, Steroids 67 (2002), 1091-1099). This information is pivotal when considering the risk of genotoxicity of all estrogen residues, not only this of estradiol. It should be recalled that all residue data on tissular estrogen were obtained by a fully validated spectro-physical procedure, discarding any doubt on false positive signals. Such reference data were never obtained at this sensitivity and precision level with any other hormones considered before.

199. As regards the criticism of Dr. Boobis of the Chakravarti et al. study concerning in particular the comment that the two major adducts formed by E2-3,4-quinone are N3Ade and N7Gua, it should be noted that both adducts are spontaneously released from the DNA (a process called depurination) but at different rates (Zahid et al., 2006): the N3Ade is depurinated much faster than the N7Gua. Therefore, the N7Gua may allow accurate DNA repair whereas the N3Ade may not be repaired properly and give rise to mutations of the type observed in the mutagenicity studies. What is important to stress, however, is that Chakravarti et al (Oncogene, 20; 7945-7953, 2001) has detected mutations in the H-*ras* gene in the skin of SENCAR mice following dermal treatment with E2-3,4-quinone, with the specific nature of the mutations detected being consistent with the expected depurination of adenine due to the formation of an E2-3,4-quinone-Adenine adduct. This is relevant to the potential mutagenicity of estradiol in humans. First, we know that oxidative metabolism of E2 to the E2-3-4-quinone metabolite occurs in human breast tissue because E2-quinone adducts to glutathione have been detected (Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003). Second, adducts of the E2-3,4-quinone with ademine and guanine have been detected in the mammary tissue of ACI rats injected into the mammary gland tissue with 4-OH E2 or E2-3,4-quinone (Carcinogenesis, 25:, 289-297, 2004). So, Dr. Boobis criticism appears to miss the important point that mutagenicity *in vivo* is now established thanks to this and the other studies cited by the European Communities in relation to Question 13 above.

200. It follows that Dr. Boobis provides a partial and selective discussion of certain aspects of these studies. The importance of these studies is however not questioned. If some of the results obtained by some of these studies are not clear or unequivocal, this simply strengthens the EC position that important gaps in our knowledge have become available recently which made the completion of a risk assessment impossible in 2000-2002 and even today for the five hormones (except for oestradiol 17β)

ANNEX F-4

COMMENTS BY CANADA TO THE REPLIES OF SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC TO QUESTIONS POSED BY THE PANEL

(30 June 2006)

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I. INTRODUCTION

1. Canada is pleased to have this opportunity to comment on the responses to the Panel's questions of the experts and international organizations. Canada expresses its appreciation to the experts and international organizations for having agreed to participate in this proceeding as scientific and technical advisors to the Panel.

2. The Panel has sought advice on the scientific and technical matters that arise in the context of the dispute between the parties over whether the European Communities (EC) has complied with the recommendations and rulings of the WTO Dispute Settlement Body (DSB) in *EC – Measures Concerning Meat and Meat Products (Hormones)*. In light of the nature of this dispute, the most relevant questions (and answers) are those that shed light on whether the scientific evidence relied upon by the EC supports its conclusions that there is a potential for the occurrence of adverse effects from the consumption of meat from cattle that have been treated with oestradiol 17β, and that there is insufficient scientific evidence to conduct an assessment of the risks from consuming meat from cattle that has been treated by any of the other five hormone growth promoters (HGP).

3. The responses provided by the experts and international organizations generally confirm the explanations of the scientific and technical issues provided by Canada in its previous submissions.[1] With some limited exceptions, these responses indicate that (1) the EC's regulatory opinions do not properly evaluate the potential for adverse effects to human health from residues of oestradiol 17β in meat from cattle treated when used for growth promotion, and (2) that the available scientific evidence is sufficient to conduct an assessment of the risks from consuming meat that has been treated with any of the remaining five HGP.

4. The issues are complex, however, and Canada submits these comments with a view to further assisting the Panel in understanding these matters. Canada has sought to identify where the experts and international organizations agree with one another and with Canada's explanations of the scientific and technical issues, to reconcile any inconsistencies among the responses received, to elaborate on certain responses that require clarification or amplification, and to address advice by certain experts that is not supported by the available scientific evidence. In several instances, Canada suggests follow-up questions that the Panel may consider asking the experts at a later date.

II. COMMENTS ON THE RESPONSES FROM THE EXPERTS

A. GENERAL DEFINITIONS

Q1. Please provide brief and basic definitions for the six hormones at issue (oestradiol 17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate), indicating the source of the definition where applicable.

5. Canada has no comment on the responses to this question provided by Drs. Boisseau, Boobis and Guttenplan other than to note that there does not appear to be any material disagreement concerning these terms.

Q2. Please provide definitions for the following terms as they relate to the hormones at issue, indicating the source of the definition where applicable: anabolic agents, steroids, steroidal oestrogens, parent compounds/metabolites, catechol metabolites, mitogenicity, mutagenicity, androgenic/oestrogenic activity, genotoxicity, genotoxic potential, carcinogenicity, and tumorigenicity. In your replies, please be sure to identify and describe any relevant differences between the terms.

6. Drs. Boobis and Guttenplan provide definitions of the terms identified by the Panel. While the responses appear to be consistent, Dr. Boobis' reply is more thorough and supported by references.

7. A few key definitions warrant highlighting. According to Dr. Boobis, carcinogenicity is the "[p]rocess of induction of malignant neoplasms", or what is commonly referred to as cancer. Neoplasms, which are new and abnormal formation of tissue, can be malignant or benign. Malignant neoplasms (cancer) pose the greatest risk to human health. In contrast, mutagenicity is the "[a]bility of a physical, chemical or biological agent to induce heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof)." Mutagenicity does not necessarily lead to the formation of malignant neoplasms (cancer).

8. Genotoxicity is the "[a]bility to cause genetic damage." Genotoxicity does not necessarily lead to mutagenicity, if the damage to the DNA is not inherited into the genotype of the affected cell. Genotoxic potential means that a compound "possesses characteristics such that it might be capable of causing genotoxicity (usually *in vivo*), based on considerations such as the results of tests in vitro."

[1] Canada First Written Submission, at paras. 86-131; Canada First Oral Statement, at paras. 41-73; and Canada Rebuttal Submission, at paras. 45-146.

Dr. Boobis emphasizes that "[i]t remains to be determined whether genotoxicity is indeed expressed *in vivo*, i.e. that the potential is realized". Thus, "potential" does not refer to the statistical likelihood that the genotoxic mode of action will occur *in vivo*, but, rather that the genotoxic mode of action is theoretically possible.

9. Combining these concepts, if a compound is only identified as having genotoxic potential, the compound is still several steps removed from carcinogenicity. The genotoxic potential will have to be realized *in vivo*, the genetic damage to the cell would have to be "fixed" into the genome created a mutated cell, the mutated cell in turn would have to replicate to form neoplasms, and the neoplasm would have to be malignant (cancer). Any one of these steps may be thwarted by the various effective and redundant defence and repair mechanisms.[2]

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

10. This question was also posed to the international bodies (Question 3). Drs. Boisseau and Boobis, as well as JECFA and Codex, responded.

11. Dr. Boobis, JECFA and Codex identify a significant number of relevant international guidance documents. A review of this documentation indicates that the development of risk assessment techniques by international organizations has been ongoing for decades. The International Program on Chemical Safety (a collaborative venture between the World Health Organization, the United Nations Environment Programme and the International Labour Organisation), as early as 1987, published a comprehensive guidance document entitled *Principles for the Safety Assessment of Food Additives and Contaminants in Food, Environmental Health Criteria 70* (EHC 70).[3] EHC 70 sets out principles and approaches to safety assessment for food additives and contaminants, consolidating of 30 years of JECFA experience. While not specific to veterinary drug residues, much of the detailed guidance is relevant to the risk assessment generally, including the assessment of veterinary drugs.

12. Building on EHC 70 and recognizing that the assessment of veterinary drug residues can pose specific issues, the WHO and FAO have issued several guidance documents outlining risk assessment techniques and procedures specific to veterinary drug residues. These include:

- JECFA, *Procedures for Recommending Maximum Residue Limits – Residues of Veterinary Drugs in Food (1987 – 1999)*, (Rome: FAO/WHO, 2000) (JECFA Procedures);[4]

- WHO, *Residues of veterinary drugs in food – WHO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives* (Geneva: January 2001);[5]

[2] For a clear explanation of the relationship between genotoxic potential and carcinogenicity, see Dr. Boobis' answer to Question 19.

[3] The International Program on Chemical Safety, *Principles for the Safety Assessment of Food Additives and Contaminants in Food*, Environmental Health Criteria 70 (Geneva: WHO,1987); online: http://www.inchem.org/documents/ehc/ehc/ehc70.htm (Exhibit CDA-43).

[4] Exhibit CDA-44 ("JECFA *Procedures for Recommending Maximum Residue Limits*").

[5] Attached to JECFA's answers to the Panel's questions.

- WHO, *Residues of veterinary drugs in food – Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives* (Geneva: August 1996);[6] and

- FAO, *Residues of veterinary drugs in food – FAO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives*, (Rome: September 2002).[7]

13. In addition to the above, Codex also identifies several relevant guidance documents, including the *Statements of principles relating to the role of food safety risk assessment*[8] and the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius Commission.*[9]

14. The JECFA *Procedures for Recommending Maximum Residue Limits* is a consolidation of JECFA's collective experience developing risk assessment techniques and methodologies for veterinary drugs from 1987 to 1999. This document confirms that many of the general risk assessment techniques and methodologies developed by international organizations are also relevant to the risk assessment of veterinary drugs.[10]

15. As JECFA points out in its response to Question 3, there is a continuous effort to update and harmonize international level risk assessment techniques for chemicals. However, the fact alone that international risk assessment techniques are continuously subject to refinement and elaboration does not, *a priori*, suggest that existing international techniques and methodologies are inadequate or problematic.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)].

16. The experts confirm the accuracy of the EC's statement referred to in the Panel's question. However, while the statement is technically correct, the experts confirm that the absence of a Codex standard does not imply an absence of internationally developed risk assessment guidelines or principles. Furthermore, the experts confirm that JECFA based its risk assessment of the hormones at issue on relevant international risk assessment methodologies and techniques.

17. Specifically, Dr. Boisseau states in his reply that:

> In the conduct of its risk assessment with respect to the hormones at issue, as for all the other pharmacologically active substances used in veterinary medicine, JECFA has followed the general rationale used by all the countries which have assessed the safety of veterinary drug residues. This rationale has been internationally harmonised through scientific conferences and it is possible to say that there was an international non written agreement on this rationale.

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[6] Exhibit CDA-45.

[7] Attached to JECFA's answers to the Panel's questions.

[8] Quoted in the answer by Codex to Question 3 addressed to the international bodies; reproduced in the *Procedural Manual of the Codex Alimentarius Commission* (15th edition), at p. 161.

[9] Annex 6 to the answers by Codex.

[10] For example, a significant portion of the general toxicological data requirements that have been established for food additives and contaminants are equally applicable to veterinary drug residues. JECFA, *Procedures for Recommending Maxium Residue Limits*, at p. 3 (Exhibit CDA-44).

18. Referring to the documents identified in his response to Question 3, Dr. Boobis also confirms that JECFA relied upon a number of relevant guidance documents in its risk assessments of the hormones at issue. Moreover, Dr. Guttenplan acknowledges that the "principles for risk assessment…were used in determining Acceptable Daily Intakes (ADI) for estradiol, progesterone, and testosterone."

19. It is apparent from the experts' answers that international organizations have expended considerable effort in developing risk assessment techniques relevant to the assessment of veterinary drugs. Much of that effort has been the result of contributions from the EC's own Member States[11] and much of the resulting guidance used as a basis for decisions taken by European regulatory authorities, including the Committee for Veterinary Medicinal Products (CVMP). Thus, any suggestion that relevant risk assessment techniques or guidance developed by international organizations for the conduct of veterinary drug risk assessments do not exist is baseless.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) and explain how they differ.

20. The responses of all four experts who replied to this question appear to be consistent with the response provided by Codex to a similar question posed to the international bodies (Question 5). In all cases, the experts and Codex identify a functional separation between risk assessment and risk management. In the context of food safety, a risk assessment is a scientific process in which data are evaluated and on this basis, together with the weight of evidence and expert judgment, a conclusion is reached as to the nature of the hazards, the potential risk to exposed individuals and the extent to which exposure is within those levels considered to be without appreciable risk.[12] The descriptions of risk assessment provided by the experts are consistent with the definition of risk assessment set out in Annex A(4) of the *SPS Agreement*, namely an evaluation of the potential for adverse effects on human health.

21. Risk management, on the other hand, is the process of weighing policy alternatives, considering the risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.[13] This description of risk management is akin to the process of identifying and selecting SPS measures appropriate to the circumstances.

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

22. This question is the same as Question 6 addressed to the international bodies. Drs. Boisseau, Boobis and Guttenplan, as well as JECFA and Codex, respond to this question. Their answers reflect principles for the conduct of a risk assessment generally accepted by the international community.

Hazard Identification

23. With slight differences, the experts and international bodies appear to agree that hazard identification involves the determination of whether an agent has the potential to cause adverse effects.

[11] For instance, the UK Department of Health and Social Security was instrumental in providing support for EHC 70.

[12] See *e.g.* Dr. Boobis, at p. 12.

[13] Codex, at p. 6.

Hazard Characterization

24. Again, with slight differences, the experts appear to agree that hazard characterization involves the quantitative and/or qualitative evaluation of the nature of the identified adverse effects caused by the agent. The experts agree that, where possible, hazard characterization should involve a dose-response assessment and a determination of whether a threshold can be established below which no adverse effects can be expected to occur.[14] The outcome of this step is the establishment of a No-Observed-Adverse-Effects-Level (NOAEL), from which an Acceptable Daily Intake (ADI) is derived. The experts' answers are consistent with JECFA's response that "[d]ose-response assessment is an integral part of each assessment and is an essential part of the hazard characterization step." As Canada has stated previously, central to this dispute is whether the EC's failure to complete this "integral part" of the risk assessment implies that the assessment conducted by the EC fails to meet the requirements of the *SPS Agreement*.[15]

Exposure Assessment

25. In terms of exposure assessment, the experts confirm that the objective of this step is to evaluate quantitatively exposure by relevant population groups to the substance under review. In order to do so, risk assessors typically use a "food basket" which is based on "available intake data at the upper limit of the range for individual consumption of edible tissues and animal products".[16] The "food basket" used by JECFA is as follows:

Muscle	300 g
Liver	100 g
Kidney	50 g
Tissue Fat	50 g
Milk	1.5 litre
Eggs	100 g

26. The Panel may wish to seek clarification from the experts on whether the food basket is adjusted to reflect estimated consumption by prepubertal populations.

Risk Characterization

27. The experts all appear to agree with the Codex definition of risk characterization: a qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on the three preceding three steps of a risk assessment. Dr. Boisseau specifics that:

> … the goal of the risk analysis for these compounds is not to assess qualitatively and quantitatively the likelihood and the gravity of the adverse effects for the health of consumers associated with the veterinary drug residues they are exposed to through the animal derived food[,] but to protect consumers' health from any adverse effect associated with these residues. [emphasis added]

[14] Dr. Boisseau, at p. 5; Dr. Boobis, at p. 13.

[15] Canada Rebuttal Submission, at para. 78.

[16] JECFA, *Procedures for Recommending Maxium Residue Limits*,, at p. 31 (Exhibit CDA-44). Also see JECFA, *Evaluation of certain veterinary drug residues in food: Fifty-second Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 893 (Geneva: WHO, 2000), at p. 67 (Exhibit CDA-16).

28. The experts confirm that to achieve the goal of no adverse effects on human health, Maximum Residue Limits (MRL) are established. The purpose of the MRL is to ensure that the exposure to residues of the veterinary drug in question consumed in edible animal products does not exceed the ADI established for that drug.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations, in your view, addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? Have they been addressed in the 1988 and 1999 JECFA risk assessments of these hormones? [see Canada's comments in para. 72 of its Rebuttal Submission]

29. The same question was put to the international bodies (Question 7). JECFA, Drs. Boobis and Boisseau respond. The experts confirm that JECFA was aware of "non-linear situations" and took these into account in conducting its risk assessment for the hormones at issue.

30. The assumption implicit in the EC's statement is that, in non-linear situations, no threshold can be established below which there is no appreciable risk. As the experts and JECFA point out, this is simply not true. JECFA explains that "probabilistic or deterministic approaches can be applied, independent [of whether] a compound is assumed to act via a threshold mechanism, i.e. non-linear" and "non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect." Thus the important issue is not linearity, as the EC has asserted, but rather whether a threshold mechanism operates and an ADI can be set. In deciphering the EC's logic, Dr. Boobis states that the EC's assertion presupposes a specific outcome to the risk assessment, *i.e.*, that no threshold can be set below which no adverse effects occur. This is simply not true. JECFA explains that "[i]n such a case, as for the hormones, a no-effect-level can be determined from which an ADI can be established."

31. In support of its "non-linearity" claim, the EC argues that "here, the risks are embedded in changes in exposure to biologically active molecules which may, within minute differences in their bioavailability, have dramatic effects, such as turning on or off complete developmental programs of the human genome, or inducing pathological conditions."[17] The EC presents no evidence that the minute increases in exposure to the hormones resulting from residues of growth promoting hormones in treated meat "turn[] on or off complete developmental programs of the human genone, or induc[e] pathological conditions." This is not surprising given that wide variation in background levels of hormones endogenously produced by humans and considerable exposure to dietary sources of hormones.

Q8. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please identify and describe any steps that are taken in the risk assessment process to build a margin of safety into the final recommendation.

32. This question is the same as Question 10 addressed to the international bodies. The description provided by the experts of the procedure followed by JECFA in the identification of ADIs and development of recommendations on MRLs appears to be consistent with JECFA's answer to Question 10. In terms of the steps taken in the risk assessment process to build in a margin of safety, Dr. Boobis describes similar steps in his answer to Question 12 when addressing scientific uncertainty. Canada would like to highlight the following:

[17] EC Replies to Questions from the Panel, Question 24. at para. 140. The EC refers to no scientific evidence in support of this assertion.

Establishment of ADI

33. The experts and JECFA have confirmed that the ADI is the highest quantity of residue that can be ingested on a daily basis over a lifetime that will not result in adverse effects to health, or, as Dr. Boobis states in response to a later question, that will pose zero risk.[18] The establishment of the ADI is a two-step process involving the determination of a NOAEL and the application of safety factors.[19] A NOAEL is established for each adverse effect. The NOAEL from the most sensitive adverse effect is used as the NOAEL for the substance.[20] "Safety factors" are applied to the NOAEL to take into account inherent uncertainties in extrapolating animal toxicity data to potential effects in human beings and variation in the human species.[21] The experts and JECFA confirm that JECFA typically uses a default safety factor of 100, representing a safety factor of 10 for extrapolation from animal to human species and a safety factor of 10 for diversity within the human population. Smaller safety factors may be justified in certain circumstances, such as where the NOAEL is derived from data from human studies. Extra factors may be applied in other circumstances such as where there is an identifiable sub-group that might reasonably be expected to be more sensitive than the group in which data were obtained (*e.g.*, children relative to adults).[22]

34. In the case of the six hormones at issue, JECFA has established the following ADIs:

Hormone	JECFA Meeting	Exhibit #	Pg.	ADI	Safety Factor
Oestradiol 17β	52nd Meeting	CDA-17	60	0-0.05 µg/kg	100
Progesterone	52nd Meeting	CDA-17	62	0-30 µg/kg	100
Testosterone	52nd Meeting	CDA-17	64	0-2 µg/kg	1000
Trenbolone Acetate	34th Meeting	CDA-30	107	0-0.02 µg/kg	100
Zeranol	32nd Meeting	CDA-29	145	0-0.5 µg/kg	100
Melengestrol Acetate	54th Meeting	CDA-31	179	0-0.03 µg/kg	200

Proposal of an MRL

35. The experts have confirmed that the MRL is a risk management tool designed to ensure that exposure to veterinary drug residues does not exceed the established ADI. In other words, if residues are within the MRL, then the ADI is unlikely to be exceeded and no adverse effects to human health are to be expected.

36. The experts and JECFA have set out various ways in which a margin of safety is built into the establishment of the MRL. In this regard, the risk assessor makes the following conservative assumptions:

- the parent substance and all its metabolites have the same potential toxicity unless demonstrated otherwise;[23]
- the parent substance and all its metabolites are considered to be bioavailable (or biologically active) unless demonstrated otherwise;[24] and

[18] Dr. Boobis, answer to Question 54.
[19] JECFA's answer to Question 10, at p. 6.
[20] Dr. Boobis, at p. 15.
[21] JECFA's answer to Question 10, at p. 6.
[22] Dr. Boobis, at pp. 14-15.
[23] Dr. Boisseau's answer to Question 13(B), at p. 10.
[24] Dr. Boisseau, at p. 23; Dr. Boobis, at pp. 14-15.

- the standard food consumption figures (the "food basket"), used to estimate exposure, overestimate actual consumption.[25]

37. As can be observed from the foregoing, JECFA has developed risk assessment techniques that build into its risk assessments a significant margin of safety.

Q9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

38. The same question was put to the international bodies as Question 11. JECFA states in its response that "[i]f there are substantial data gaps and important information missing, JECFA can not establish an ADI." [emphasis added] This confirms Canada's statement quoted in the question was correct. Thus, given that JECFA established ADI for all six hormones at issue, it is reasonable to infer that the record was complete and sufficient for all hormones in question.

39. The experts who responded to this question, Dr. Boisseau and Dr. Boobis, confirm that Canada's statement is correct as a general rule. Dr. Boobis identified a number of exceptions in which JECFA might issue an ADI without a complete dataset. As he explains, the "critical issue is whether a sufficiently cautious default can be adopted in the absence of certain information." He concludes that "JECFA would require a complete data base unless it could adopt default assumptions that would if anything lead to a more conservative risk assessment than would be the case otherwise".

Q10. In paras. 129 and 168 of its Replies to the Panel Questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not". Does Codex have risk management options other than (1) the establishment of an MRL, (2) establishing that an MRL is not necessary or (3) no recommendation?

40. The same question was put to the international bodies as Question 12. JECFA's answer clarifies that its role is to conduct risk assessments. It will only consider the health impact of specific risk management options, if requested to do so by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). The response by Codex to Question 12 indicates that it is not necessarily limited to the three risk management options listed in the question, and mentions the possibility of developing "codes of practice" through the CCRVDF.

Q11. What should, in your view, be the components of a qualitative risk assessment, compared with a quantitative risk assessment? [see para. 82 of Canada Rebuttal Submission]

41. The experts with specific expertise on risk assessments of veterinary drugs explain that a qualitative risk assessment may be conducted under certain limited circumstances. Both Dr. Boisseau and Dr. Boobis agree that a qualitative risk assessment should comprise the main steps of a conventional risk assessment, including hazard identification, hazard characterization and exposure assessment. Both experts also agree that if the mode of action is such that a dose-response relationship cannot be established and, thus, no safe intake threshold can be set, then a quantitative dose-response assessment is not necessary. However, Dr. Boobis explains that even where the need for detailed dose-response analysis would be questionable, a risk assessment still needs "scientific rigour", a

[25] Dr. Boisseau, at p. 7.

statement supported by the Appellate Body's description of the risk assessment process as characterized by "systematic, disciplined and objective enquiry and analysis."[26]

42. Dr. Boisseau provides examples of where JECFA has based its conclusions on a qualitative risk assessment and declined to recommend an ADI (*e.g.*, chloramphenicol and nitroimidazole). Both Dr. Boisseau and Dr. Boobis also confirm in subsequent answers that, in respect of the hormones at issue in this dispute, a dose-response assessment can be undertaken and a safe threshold (ADI) can be established for each hormone.[27] Thus, it can be inferred that, according to internationally developed risk assessment techniques, a risk assessment for these substances that does not include a dose-response assessment would be incomplete.

43. Dr. Cogliano also responds to this question with references to IARC's practice in developing its monographs. However, the type of assessment to which Dr. Cogliano refers only satisfies the first element of a risk assessment contemplated by the *SPS Agreement*, which includes both the identification of adverse effects arising from the substance at issue and the evaluation of the potential of occurrence of such effects. In this regard, it is important to recall the Appellate Body's conclusion regarding previous IARC Monographs relied upon by the EC in the first hormones dispute. After citing the Panel's conclusion that the IARC Monographs were "in the nature of general studies of…the carcinogenic potential of the named hormones" and have not "evaluated the carcinogenic potential of those hormones when used specifically *for growth promotion purposes*"[28], the Appellate Body, in *EC – Hormones*, concluded as follows:

> We believe that the above findings of the Panel are justified. The 1987 IARC Monographs and the articles and opinions of individual scientists submitted by the European Communities constitute general studies which do indeed show the existence of a general risk of cancer; but they do not focus on and do not address the particular kind of risk here at stake – the carcinogenic or genotoxic potential of the residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes – as is required by paragraph 4 of Annex A of the *SPS Agreement*. Those general studies, are in other words, relevant but do not appear to be sufficiently specific to the case at hand.[29]

44. It is also worth noting that Codex has estimated general principles in relation to the use of quantitative information. For instance, the Codex *Statements of principles relating to the role of food safety risk assessment* include requirements that "[f]ood safety risk assessment should be soundly based on science, … ", and that "[r]isk assessment should use available quantitative information to the greatest extent possible …" [emphasis added] Moreover, paragraph 20 of the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* restates the same principles while recognizing that a risk assessment may also take into account qualitative information. Paragraph 23 of the *Working Principles* also provides:

> Constraints, uncertainties and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner. Expression of uncertainty or variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable. [emphasis added]

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[26] *EC – Measures Concerning Meat and Meat Products (Hormones)*, Report of the Appellate Body, WT/DS26/AB/R, WT/DS48/AB/R, adopted February 13, 1998, at para. 187 (*EC – Hormones*).

[27] See answers to Questions 36 and 37.

[28] *EC – Hormones*, Report of the Appellate Body, at para. 199.

[29] *Ibid.*, at para. 200.

Q12. How is scientific uncertainty addressed in risk assessments in general? With respect to the assessment of risks from the consumption of meat treated with the growth promotion hormones at issue, how has scientific uncertainty been considered by JECFA/Codex ? How does it differ from the way it has been considered by the European Communities in its assessment of risks from the consumption of meat treated with the growth promotion hormones at issue?

45. Both Drs. Boisseau and Boobis explain the numerous ways in which scientific uncertainty is addressed in a risk assessment. Dr. Boobis' response is worth quoting at length:

> One way of dealing with uncertainty is [1] to default to the worst case in the absence of evidence to the contrary. Hence, the most sensitive relevant endpoint in the most sensitive species is used as the basis of the risk assessment. [2] In extrapolating to humans a default factor of 10 is used to allow for species differences, which assumes that humans are more sensitive than the experimental species. [3] A further factor of 10 is included for interindividual differences. These differences may be due to gender, genetics, life stage or other factors. [4] However, to some extent such differences have already been taken into account in the choice of endpoint, as this will usually represent the most sensitive lifestage, gender and to some extent genetics by using data from the most sensitive species. [5] Where there are additional uncertainties, such as no NOEAL or the absence of a non-critical study, an additional safety factor will be included, and this is almost always conservative, as when the data gaps have been completed, the appropriate safety factor is almost always less than that used to account for these data gaps. [6] The residue may be assumed to be all as active as the most active moiety, which is almost always a conservative assumption. [7] Dietary intake is based on conservative data for food consumption. [8] It is also assumed that all meat that could contain veterinary drug residue will contain the residue and that this will be present at the high end of the range (MRL or other appropriate level). [9] In respect of the ADI, the assumption is that intake will be at this high level for a lifetime, when in reality there will be occasions when little or no meat is consumed or that which is consumed contains less or even no residue. In their risk assessment of the hormones, JECFA applied all of these approaches to dealing with the uncertainty.

46. Dr. Boisseau indicates that the EC "did not consider any scientific uncertainty", because it had decided as a matter of "principle" that it was not possible to establish an ADI for genotoxic substances. Clearly, however, this "principle" is one of selective rather than general application, if one considers that the EC knowingly allows its population to consume, without so much as a warning, the very same "genotoxic" substance (*i.e.*, oestradiol 17β) naturally present in many dietary sources (*e.g.*, milk, eggs, meat) and in oral contraceptives, at levels many times higher than that which would be present as residues of growth promotants.

B. ASSESSMENT OF OESTRADIOL-17B

Q13. To what extent, in your view, does the EC risk assessment identify the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol 17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice? To what extent does the EC risk assessment evaluate the potential occurrence of these adverse effects?

47. Drs. Boisseau, Boobis and Guttenplan chose to answer this question, and all of them indicate that the EC's "risk assessment" (*i.e.*, the three SCVPH opinions) was deficient in one manner or

another in its evaluation of the potential occurrence of adverse effects (whether carcinogenic, genotoxic or other) from the consumption of residues of oestradiol 17β in meat from treated animals.

48. Dr. Boisseau acknowledges the general international agreement that oestradiol 17β is associated with "carcinogenic potential", but also confirms what Canada has explained in its submissions: that this potential is due to the hormonal effect of estrogens,[30] which requires "prolonged exposure to high concentrations" for adverse effects to occur. Exposure to residues of these hormones from meat from treated cattle does not generate the "high concentrations" considered by Dr. Boisseau and others to be required for these effects to occur.

49. Dr. Boisseau further confirms that, despite the growing acknowledgement that oestradiol 17β may have "genotoxic potential", there is no evidence that this potential is realized *in vivo* (as opposed to *in vitro*). He points out that, as a result of what must be done to observe a genotoxic effect (*i.e.*, use far higher than realistic doses of the parent compound with an assumption that the toxicity is the same as that for residues), such tests are more useful for identifying modes of action than for assessing dose-response relationships. He therefore disagrees with the EC, as do most other experts and international scientific bodies, that no threshold can be set for substances for which "genotoxic potential" has been identified.

50. Dr. Boisseau also shares Canada's concern that the EC did not conduct any "quantitative risk assessment" of other adverse effects, known to be dose-dependent, that would lead to the establishment of thresholds and ADIs that would differ from those established by JECFA. The quantitative assessment referred to here is not the same as that contemplated by the Appellate Body when it found that a risk assessment need not quantify the risk.[31] Rather, Dr. Boisseau refers to analyses of the dose-response relationship that is completely absent from the EC's opinions, but which is a crucial component of internationally accepted risk assessment techniques and is essential if the EC is to demonstrate that existing international standards are insufficient to achieve its appropriate level of protection.

51. Dr. Boobis also cites the flaws in the EC opinions as a risk assessment, in particular that the analysis "focused primarily on hazard identification". He confirms what Canada has explained in its submission,[32] that there was "little in the way of hazard characterization and no independent exposure assessment". Without the data generated in these steps, which have been shown in responses to previous questions to be necessary components of a risk assessment, Dr. Boobis advises the Panel that "it was not possible [for the EC] to complete the risk characterization phase". Most importantly, Dr. Boobis indicates that the EC "essentially stopped" the assessment of risk after it concluded that no thresholds of exposure could be established. In light of the later responses of all the experts about the issue of thresholds,[33] this observation by Dr. Boobis is critical: it means that the EC decision not to conduct a complete risk assessment was based on a conclusion that is not supported by the evidence.

52. For his part, Dr. Guttenplan similarly finds that the EC's evaluation of the potential occurrence of adverse effects is "weak", even as he accepts that the EC did identify potential adverse effects. However, identifying potential adverse effects (*i.e.*, the hazard identification) is only the starting point of a valid risk assessment. As for the remaining components of such an assessment, Dr. Guttenplan points to several deficiencies in the EC's opinions (*i.e.*, limited utility of animal models, absence of epidemiological studies, *etc*.) and concludes that "little can be inferred about the potential occurrence of the adverse effects".

[30] Canada First Written Submission, at paras. 95-97; Canada Rebuttal Submission, at paras. 90-96.
[31] *EC – Hormones*, Report of the Appellate Body, at paras. 186-187.
[32] Canada Rebuttal Submission, at paras. 76-85.
[33] See Canada's comments below on the experts' responses to questions 16-19.

Q14. In your view, does the risk assessment undertaken by the European Communities on oestradiol 17β follow the Codex Guidelines on risk assessment, including the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization with respect to oestradiol 17β?

53. In addition to their responses to the more general question above, Drs. Boisseau, Boobis and Guttenplan also agree with Canada that the EC failed to follow the Codex guidelines on risk assessments. The experts share Canada's concerns that the EC (and SCVPH) took significant and unjustified short-cuts in the conduct of its risk assessment.[34]

54. Dr. Boisseau is very critical of the EC's decision not to follow the Codex guidelines, concluding that the EC's own science did not justify the abandonment of these guidelines. At most, Dr. Boisseau concedes that the scientific studies relied upon by the EC indicate that it should have refined its approach to assessing exposure to hormone residues, not abandon the entire risk assessment methodology. But as Canada has indicated in its submissions,[35] the EC has done very little that resembles an exposure assessment.

55. Dr. Boobis states simply that the EC did not follow Codex guidelines (which include the four steps), adding that even if the EC concluded that oestradiol 17β was genotoxic – a conclusion with which Dr. Boobis disagrees in his response to Questions 15, 18 and 19 – the EC should still have followed all four steps.

56. Dr. Guttenplan also finds it difficult to give the EC's risk assessment anything more positive than a "mixed rating". For many of the same reasons advanced by the others, Dr. Guttenplan finds fault in the EC's hazard characterization and risk characterization, the first because of the questionable relevance of studying hamster kidneys for the task at hand and the second because it is "qualitative at best", and not based on any data or confirmed by epidemiological studies. Moreover, Dr. Guttenplan's limited support for the EC's exposure assessment is left unexplained; he simply declares it to be "thorough", which is itself an odd declaration in light of the EC's own admission that it did not, because it could not, conduct an exposure assessment.[36]

C. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

Q15. Does the identification of oestradiol 17β as a human carcinogen indicate that there are potential adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes? Does your answer depend on whether good veterinary practices are followed? [see para. 206-207 of EC Rebuttal Submission (US case), para. 121 of EC Rebuttal Submission (Canada case), paras. 97-98 of EC Replies to Panel Questions, paras. 76-77, 150 and 155-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission]

57. Drs. Boisseau, Boobis and Guttenplan all agree with Canada that the mere identification of oestradiol 17β as a carcinogen is not itself sufficient to conclude that there are potential adverse effects when consumed as residues in meat from treated animals. Not only is the evidence of the substance's carcinogenicity in general not indicative of carcinogenicity of the substance from a given source, but most of the experts conclude affirmatively that there would be "no appreciable risk" of adverse effects from exposure from this one minimal source of oestradiol 17β.

[34] Canada Rebuttal Submission, at para. 86.
[35] *Ibid*., at paras. 83-85.
[36] EC Rebuttal Submission, at para. 141; 1999 SCVPH Opinion, at p. 20 (Exhibit CDA-2).

58. The experts arrive at this conclusion following the tried and tested methods of the international scientific community. Dr. Boobis' explains the relationship between findings of carcinogenicity in general and adverse effects from this one source in particular by stating that "the entire basis of risk assessment in [*sic*] based on the fact that there is a relationship between dose and effect"; and second, that a "key consideration in the risk assessment is whether there is a threshold in the dose-response". Applying these two principles to oestradiol 17β, which is naturally produced in the human body, Dr. Boobis considers that the main task is to determine whether the additional exposure to hormones from meat from treated animals changes the circulating levels of the hormone. The answer given by JECFA (and not contradicted by the EC) is that it does not; therefore, even though oestradiol 17β is considered a human carcinogen when exposure is prolonged and significantly greater than the ADI, exposure to it from this single source does not present such risks.

59. The experts do not agree on whether the answer would be different if good veterinary practice (GVP) was not followed. On the one hand, Drs. Boisseau and Guttenplan indicate that there might be a potential for adverse effects if GVP were not followed. As general answers, they are not really surprising. These experts are simply applying a general scientific principle that changes in assumptions in the course of predicting an outcome (*e.g.*, cancer) may change the prediction. While neither expert would guarantee that the outcomes would be the same if GVP had not been followed, they did not state categorically, nor could they have, that the failure to follow GVP will create the potential for adverse effects to occur. In fact, even the studies on this issue submitted by the EC demonstrate that multiple hormone implants resulted in residues that were still less than the ADIs.[37]

60. Whereas the answers of Drs. Boisseau and Guttenplan are based on general principles about the effect of changing assumptions, Dr. Boobis deals more specifically with the conditions of exposure from the failure to follow GVP. He states that failure to follow GVP would only affect the cancer risk if it resulted in exposure levels above the ADI, and even then it would have to be on a "regular basis". Since he believes that neither of these conditions will be met, Dr. Boobis advises that the failure to follow GVP "would not be associated with any increase in risk of cancer".

61. Dr. Boobis' response suggests an obvious point, but one worth emphasizing: that it is not the conditions under which the hormones are administered that cause adverse effects, but the resulting hormone exposure levels, which depend on many factors. This reinforces the Appellate Body's findings that the EC has to demonstrate through an assessment of the risk arising from the failure to follow GVP that it increases the risk of adverse effects.[38] As the advice from the experts confirms, the EC has not done so.

62. For his part, Dr. Cogliano simply asserts, without explanation or support, that the identification of oestradiol 17β as a human carcinogen indicates consuming it via meat from treated cattle has the potential to cause adverse effects. His answer seems to suggest that he believes there is no threshold below which adverse effects will not occur, a point which he does not support and which is also contrary to the findings of JECFA, Codex and his colleagues who also answered this question. His point that adverse effects depend on the "presence of hormones in the meat that people consume" is also inconsistent with the fact that hormones are already present in meat regardless of whether it is derived from treated cattle or non-treated cattle.

Q16. Does the scientific evidence relied upon in the SCVPH Opinions support the conclusion that carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity? [see para. 148 of the EC Replies to Panel Questions and paras. 35-40 and 46 of US Rebuttal Submission]

[37] Canada Rebuttal Submission, at para. 110 and Exhibit EC-52.
[38] *EC – Hormones*, Report of the Appellate Body, at paras. 205-208.

63. Drs. Boisseau and Boobis agree with Canada that any potential carcinogenic effects of these hormones are related to their hormonal activity, which is dose-dependent and exhibits a threshold exposure level below which these effects will not occur. More importantly, they agreed that the evidence relied upon by the EC does not support the conclusion that adverse effects will arise from anything other than the hormonal activity of these substances, such that existing international standards will be insufficient to meet the EC's level of protection.

64. Dr. Boobis provides extensive analysis of the EC's controversial theory that carcinogenic effects of these hormones may be caused by a mechanism other than hormonal activity, in particular a genotoxic mechanism. Dr. Boobis acknowledges that some studies demonstrate that the hormones may be genotoxic *in vitro*, but categorically rejects, with supporting evidence, that this has been demonstrated *in vivo*. He advises that "guidelines for genotoxicity testing require confirmation of an *in vitro* positive result using an appropriate *in vivo* assay" for such *in vitro* positive result to have any validity. Dr. Boobis provides a number of explanations of why this *in vivo* confirmation is so critical, in particular because the *in vitro* conditions that allow the genotoxicity to be observed do not contain the many defence and repair mechanisms that would exist *in vivo* to prevent cell damage from occurring. The failure to observe positive genotoxicity test results *in vivo* confirms that these defence and repair mechanisms operate to ensure that there is a threshold exposure below which genotoxicity will not occur.

65. Only Dr. Guttenplan attempts to support the EC's conclusion, but he does so with no analysis of his own, choosing instead simply to cite the EC's regulatory opinions. In simply referring to the conclusions of the SCVPH, Dr. Guttenplan has in fact failed to adequately answer the question, which was not whether the SCVPH had concluded that there were non-hormonal adverse effects, but whether the scientific evidence relied upon by the SCVPH supported that conclusion.

Q17. Could you comment on Canada's statement that "the studies commissioned by the European Communities also failed to find evidence of "catechol metabolites" – that is the oestradiol metabolites identified as the source of the genotoxic potential – in meat from treated animals"? What would be the implication of an absence or presence of catechol metabolites? [see para. 102 of Canada Rebuttal submission, EC Exhibit 51A]

66. Drs. Boisseau and Boobis confirm the evidence that catechol metabolites are largely absent in meat from treated animals, and that even if such metabolites were present in small quantities (which they acknowledged may be possible), it would not be enough to make the genotoxic potential of oestradiol 17β an issue with respect to residues in meat from treated animals.

67. Dr. Boobis advises that the absence of catechol metabolites confirms the effectiveness of the mechanisms for detoxification and elimination of these metabolites *in vivo*. He further confirms that the formation of such metabolites in meat would only be relevant to the risk assessment if it were true that catechol metabolites were responsible for adverse effects and if it were true that there is no threshold for any effects for which they are responsible. In his response to this and other questions, Dr. Boobis advises that neither of these are the case, so the presence or absence of catechol metabolites preformed in meat does "not impact on the risk assessment".

68. Dr. Guttenplan's seemingly contrary acknowledgement that "only very small amounts of catechol metabolites were detected" overstates the case. As other experts confirm in greater detail, the study commissioned by the EC that looked at the issue observed that "no metabolites coming from the catechol oestrogen biosynthesis could be isolated" and that "metabolic studies performed *in vivo* … and *in vitro*… failed to demonstrate a significant aromatic hydroxylation activity that would lead to catechol oestrogen derived metabolites".[39] In other words, contrary to Dr. Guttenplan's claim, catechol

[39] Exhibit EC-51A, at p. 18.

metabolites have not been found in meat from treated animals, at least not in detectable quantities, and to the extent that they exist in undetectable quantities, they are not present in sufficient quantities to create a genotoxic potential. In light of the discrepancy between the explicit conclusions of even the EC evidence on this issue and the unsupported claim of Dr. Guttenplan, the Panel may wish to ask him to support his claim.

Q18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol 17β is genotoxic. Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see paras. 118-119 of EC Rebuttal Submission (US case), paras. 123-124 of EC Rebuttal Submission (Canada case), paras. 87-91 and 153-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission, and paras. 90-97 of Canada Rebuttal Submission]

69. Drs. Boisseau and Boobis both confirm Canada's explanation that the EC has failed to demonstrate that oestradiol 17β is genotoxic *in vivo*.[40] They acknowledge what other reputable international scientists and scientific authorities now see as the "genotoxic potential" of oestradiol 17β, but deny that this "potential" is relevant *in vivo* at doses to which humans are exposed from consuming meat from treated animals.

70. Dr. Boobis reiterates his detailed analysis in response to Question 15 that sets out the many reasons for which genotoxic potential identified in *in vitro* will not be confirmed *in vivo*. In particular, he highlights the important point that the genotoxicity that has been "observed in vitro would be expected to exhibit a threshold." The EC's conclusion that there is no threshold below which genotoxicity will not occur runs directly counter to this advice, and is therefore not supported by the scientific evidence.

71. Dr. Boisseau also highlights an attempt by the EC to misrepresent certain of JECFA's findings. In particular, he points to the EC's efforts to represent JECFA's findings about the "genotoxic potential" of oestradiol 17β, combined with its decision to establish an ADI, as a finding that oestradiol 17β <u>is</u> "genotoxic". Dr. Boisseau correctly points out in his answer to Question 13 that there is a difference between a substance having "genotoxic potential" and it being "genotoxic", confirming that JECFA has never considered that oestradiol 17β is "genotoxic". Dr. Boisseau then explains the rationale behind JECFA's decision to adopt an ADI in 1999, pointing to the need to place exposure to oestradiol 17β from this source into context. His explanation was confirmed by JECFA in its answer to Question 20. Citing exposure values identified by JECFA, Dr. Boisseau advises the Panel that exposure to residues of the three natural hormones remains a mere fraction of the ADI (conservatively estimated between 0.03% and 4.0%, depending upon the substance). In other words, the EC claims to the contrary notwithstanding,[41] JECFA's establishment of an ADI for the three natural hormones was not related to its findings about "potential genotoxicity". In fact, just the opposite is true: JECFA would not have established ADIs at all if it considered the hormones to be genotoxic *in vivo*.

72. For their part, Drs. Cogliano and Guttenplan both suggest that the EC has demonstrated that oestradiol 17β is genotoxic, but neither of them does so with reference to supporting scientific evidence. Dr. Cogliano simply repeats the EC's assertion that it is, and endorses an excerpt from the EC Rebuttal Submission that was itself from a report of the UK Veterinary Products Committee

[40] See Canada First Written Submission, at paras. 95-98; also see Canada Rebuttal Submission, at paras. 86-98.

[41] EC Rebuttal Submission (Canada case), at paras. 100-101.

(VPC).[42] However, the EC neglected to include, when quoting from that report, the very next paragraph, which concluded that:

> [a]lthough there is evidence that oestrogen metabolites may be directly genotoxic *in vitro*, *in vivo* their formation is affected by opposing activation and inactivation metabolic pathways, the presence of anti-oxidants and DNA repair capacity and thus it is likely this genotoxicity will have a thresholded response.[43]

73. Even as Dr. Cogliano endorses the EC's selective quote from the VPC Report, he also appears to understand and accept the broader context of that quote when he admits that "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans". This observation brings him in line with Drs. Boisseau and Boobis, who explain that there is a threshold exposure below which genotoxicity will not occur.

Q19. The European Communities states that "... it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol 17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance". Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case), paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]

74. Drs. Boisseau and Boobis (and, to a lesser extent, Dr. Cogliano, but not Dr. Guttenplan) explicitly confirm the main point that Canada has made from the beginning of this dispute: that for substances that are endogenously produced by the human body, there simply must be a threshold below which no adverse effects are observed, or else humanity would have been wiped out by cancer millennia ago. This simple reality, repeatedly ignored by the EC, but stressed time and again by experts from around the world,[44] contradicts directly the EC's claim about the genotoxicity of the three natural hormones, and its corresponding claim that no threshold can be established.

75. Even though JECFA acknowledged that oestradiol 17β may have genotoxic potential, it decided to establish an ADI. If there had been no threshold below which exposure to the substance would be safe, JECFA would not have been able to establish an ADI. More recently even, the European Food Safety Authority (EFSA) (the successor to the SCVPH) has recognized thresholds for genotoxic substances when it concluded that, "based on the current understanding of cancer biology there are levels of exposure to substances which are both genotoxic and carcinogenic below which cancer incidence is not increased (biological thresholds in dose-response)".[45]

76. As pointed out by many of the experts in their responses, the consensus among the experts on the issue of thresholds is based not only on their scientific understanding of the modes of action of the

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[42] EC Rebuttal Submission (Canada case) at para. 124. See also UK, Veterinary Products Committee, *Risks Associated with the Use of Hormonal Substances in Food-Producing Animals: Draft report of the UK Veterinary Products Committee*, May 2005 (UK VPC Draft Report), at p. 27 (Exhibit CDA-26).

[43] *Ibid*.

[44] Not only do the experts relied upon by the Panel confirm this, but this conclusion has been confirmed by all international bodies that have addressed the issue. See, for example, VPC and JECFA.

[45] EFSA, *Opinion of the Scientific Committee on a Request from EFSA Related to a Harmonised Approach for Risk Assessment of Substances which are both Genotoxic and Carcinogenic* (Request No. EFSA-Q-2004-020, adopted October 18, 2005) (*The EFSA Journal, 282, 1-31, 2005*), at p. 18 (Exhibit CDA-46).

substances but also on the absence of any epidemiological studies that demonstrate a relationship between exposure to hormones and adverse health effects.

77. Dr. Cogliano's response does not directly address the question. He offers his view that the difference between the parties to the dispute is simply one of differing assumptions about the nature of genotoxic mechanisms. But the question is not about what Canada or even the EC assume about genotoxic mechanisms, but rather which assumption is supported by the science, in particular whether the "genotoxic potential" of these hormones exhibits a threshold below which it will not be realized *in vivo*. He also does not cite any evidence that supports the EC's conclusion that no such threshold exists.

78. Dr. Guttenplan appears to be more explicit in his suggestion that the science relied upon by the EC supports its conclusion, but his answer is at the same time contradictory. In admitting that "repair enzymes are unlikely to be saturated" at physiological levels, he seems to suggest that there is a level at which repair will always occur. He then goes on to say that "[f]or any toxin the dose determines the risk". These two statements together suggest that at the dose to which consumers are exposed to oestradiol 17β residues from treated meat, the "genotoxic potential" of these hormones is not relevant. This is consistent with what the other experts have indicated: that there is indeed a threshold below which these hormones are safe.

Q20. In your view, how do the European Communities' conclusions above relate to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary"? To what extent, in your view, has JECFA's conclusion that oestradiol "has genotoxic potential" affected its recommendations on this hormone?

79. Drs. Boisseau, Boobis and Guttenplan all consider the EC's conclusions about the absence of thresholds to be inconsistent with the Codex standards, whereas it remains somewhat unclear what Dr. Cogliano thinks about this issue. However, to the extent that most of the experts found that the EC's conclusions on the matter are unsupported by the evidence and are "questionable", they support the existing Codex standards.

80. Dr. Boobis elaborates on the concept of "incremental risk"; first by clarifying what in his mind is the more important issue of whether low levels of exposure affect "circulating levels". He makes three important points: (1) homeostatic control mechanism combined with low bioavailability means there is a "range of exposures for which there are compensatory alterations in endogenous levels"; (2) depending on endogenous levels, which vary by physiological state, some increments in exposure may "perturb endocrine effects", but these exposures would have to be above the ADI; and (3) genotoxic effects, to the extent that they will occur at all, will respond more to the natural variations in endogenous levels than the small changes in these levels that might arise from hormones from meat from treated animals. All of these points support the conclusion that there are clear thresholds for exposure to exogenous sources of substances that are also produced endogenously in variable amounts.

81. The experts' answers also confirm again that even though JECFA acknowledged that oestradiol 17β has "genotoxic potential", this acknowledgement did not generate concern about the safety of the substances and therefore did not affect its recommendation. JECFA essentially did not consider that this "genotoxic potential" was relevant to the carcinogenic effects of oestradiol 17β, which it considered dependent on hormonal activity.

82. For his part, Dr. Guttenplan attempts to justify the EC's conclusion with reference to new "areas of concern, such as developmental effects". However, Canada has some difficulty understanding the relationship Dr. Guttenplan seems to be drawing between the purported inability to

set thresholds for genotoxic substances and the identification of new concerns that appear to result from hormonal activity. Dr. Guttenplan seems to be using new concerns about one type of adverse effect (developmental effects) to demonstrate that concerns about the occurrence of another type of adverse effect (genotoxicity) are justified. The Panel may wish to ask Dr. Guttenplan to elaborate on the relationship he suggests in this response.

Q21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol 17β, when consumed as residues in meat have genotoxic potential? Does your answer depend on whether good veterinary practices are followed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see, *inter alia*, the SCVPH Opinions and paras. 63, 83, 89-91 and 93 of US First Submission, paras. 131-136 of Canada Rebuttal Submission]

83. Drs. Boisseau, Boobis and Guttenplan all refute the EC's claims about the potential genotoxicity of the other five hormones. Drs. Boisseau and Boobis survey the various tests by which these substances failed to show genotoxicity (the former in his answer to Question 16), and Dr. Guttenplan simply states generally that there is "no conclusive evidence presented by the EC" that they have genotoxic potential.

84. Whereas Drs. Boisseau and Boobis both indicate without qualification that the failure to follow GVP would not affect the "genotoxic potential" of the five hormones, Dr. Guttenplan's advice on this matter contradicts his advice given in response to other questions. In some of his other responses, he seems to support the EC's contention that no threshold can be established for substances that are genotoxic. At the same time, he provides in his response to this question that genotoxic effects will be "minimized by good veterinary practice". To the extent that the purported risks from failure to follow GVP are that cattle (and ultimately consumers) will be exposed to higher doses, Dr. Guttenplan seems to be suggesting a dose-response relationship between exposure to hormones and genotoxicity. The Panel could ask him to clarify his views on whether there is a dose-response relationship.

Q22. How would you define *in vivo* DNA repair mechanisms? How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat? Does your answer depend on whether good veterinary practices are followed in the administration of these hormones? To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones? Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why? [see paras. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission]

85. Drs. Boobis and Guttenplan both extensively discuss the effectiveness of DNA repair mechanisms in what the former calls a "flexible and very efficient DNA repair process" and what the latter considers a mechanism with "considerable redundancy". They also both agree that the repair mechanisms that operate to repair the "considerable oxidative DNA damage" (Dr. Boobis) caused by endogenous processes are as effective for damage caused by exogenous agents.

86. Importantly, Dr. Boobis points out that because of DNA repair mechanisms, the creation of DNA adducts does not in itself always indicate that mutations will occur, let alone malignant neoplasms (*i.e.*, cancer). He further confirms that the kind of DNA damage that might be expected from hormones from meat from treated animals (*i.e.*, active oxygen) is also the kind of repair mechanism that is "amongst the most efficient".

87. For his part, Dr. Guttenplan makes some unsupported statements, in particular when he suggests that repair mechanisms are "not really relevant" to a risk assessment of oestradiol 17β because the repair will not be different than for other types of damage. He does not attempt to describe the "other types of damage" and whether repair of these other types of damage means that such damage does not lead to adverse effects. In the absence of a specific assessment of the effectiveness of the repair mechanisms for comparable types of damage, the statement that they are comparable is not helpful.

88. Quite apart from the lack of clarity in Dr. Guttenplan's response, it is inconsistent with the more thorough advice provided by Dr. Boobis. The central issue differentiating JECFA's conclusion that even though oestradiol 17β has "genotoxic potential" it is possible to establish an ADI, on the one hand, and the SCVPH's conclusion that oestradiol 17β is genotoxic and therefore no threshold exposure can be determined, on the other, is the degree to which damaged DNA, if indeed it is damaged, is repaired and adverse effects avoided. Far from being "not really relevant", therefore, this issue is one of the most relevant issues to the resolution of the controversies surrounding the safety of these hormones. It is therefore also central to the issue of whether the EC has conducted a valid risk assessment.

89. With respect to whether the EC had failed to take into account these repair mechanisms in its evaluation, Dr. Guttenplan considers that it failed to do so. Ultimately, to the extent that the SCVPH takes so many short-cuts in its opinions on the basis that the hormones are seen to be genotoxic, the failure to address the role of mechanisms that counter this genotoxic potential is a critical shortcoming. Ignoring such evidence results in a significant overestimation of the risk, to the point of concluding there are risks where none exist.

Q23. To what extent is it necessary or possible to take into account the "long latency period" of cancer in the conduct of a risk assessment, which is supposed to assess carcinogenic effects of these hormones when consumed in meat? Have the hormones in dispute been used as growth promoters over a sufficient number of years for an assessment of their long-term effects on human health to be made? [see para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case)]

90. There is both agreement and disagreement between the experts who answered this question (Drs. Boisseau, Boobis, Cogliano and Guttenplan) on the importance of cancer's long latency periods to the conduct of risk assessments that purport to identify cancer risks from hormones in meat. On the one hand, the experts tend to agree that the hormones in question have been in use long enough as growth promoters (a minimum of 20 years, according to some) for any long-term health effects to manifest themselves. On the other hand, they disagree about whether it is possible to positively identify the use of these hormones for growth-promotion purposes as the source of any observed adverse health effects. Dr. Cogliano does not weigh in on either of these points, confining himself instead to the observation that it is "definitely necessary" to take long latency periods into account in general, a point not disputed by any other expert.

91. Dr. Guttenplan advises that it is possible to identify a relationship between hormones consumed in meat and carcinogenic effects, but he does not explain how this would be accomplished. He provides no information on how to account for the fact that the populations he says would be studied to observe the relationship would also be exposed to many other sources of hormones other than that consumed through meat from treated animals, such that it would be very difficult to identify any causal relationship between the effect and the specific source.

92. Dr. Boobis is sceptical, but does seem to suggest that it might be possible with a well designed study involving "extremely large populations to detect any increase in cancer incidence". Dr. Boisseau is even more sceptical that a relationship can be identified with any certainty, finding not

only that it is not possible to study such a relationship, but it is not even "useful". Drs. Boisseau and Boobis explain their scepticism in two separate, but related, ways: the former says it would be impossible to discriminate between different factors in allocating responsibility (see also the experts' responses to the next question on confounding factors); the latter says that since the risk from such a small dose is so minimal, "it is questionable whether an increase in risk, even if it existed, could be detected in exposed populations." In other words, epidemiological studies are of little use in risk assessments of hormones in meat from treated cattle.

93. The answers from these two experts confirm again the essential point: that exposure to residues of hormones in meat from treated animals is only a small fraction of the overall exposure to the substance from a variety of sources, including that produced endogenously within the human body. Given the wide variety of sources of, and variability of exposure to, hormones, any correlation observed between exposure to hormones and adverse effects cannot be attributed to the single source of hormones that comes from residues of hormones in meat from treated animals. Nothing in the SCVPH's opinions, in the scientific evidence submitted by the EC, or in the answers of the experts supports a conclusion other than this.

Q24. To what extent is it possible to identify possible co-founding factors causing cancer and attribute them to identified sources? What are the implications of these factors for the conduct of a risk assessment evaluating the adverse affects caused by residues of growth promoting hormones in meat? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

94. Drs. Boisseau, Boobis, Cogliano and Guttenplan all agree that it is extremely difficult to attribute causal roles to different confounding factors in the study of the causes of cancer, even as some of them advise that it is at least possible to identify what some of these factors may be. According to Dr. Boobis, this would be particularly the case in the circumstances of these hormones, where "the risk from the confounder is appreciably greater than the risk of the exposure of interest".

95. To the extent that any of the experts respond to the second part of the question, they seem to suggest that the difficulty with attributing causality to a specific factor reduces the value of epidemiological studies in risk assessments of the nature under review here (*i.e.*, where the source of the agent under review comprises such a small amount of overall exposure and the adverse effects have multiple causes). Dr. Boobis offers the view that confounding factors do not affect the risk assessment, but the "interpretation of the data used in the risk assessment", which Canada understands to mean that all causal factors should be taken into account, and not just single factors.

96. Contrary to advice from the experts that it is extremely difficult to isolate confounding factors in circumstances such as these, the EC has claimed that it has done just that. It has taken observed adverse effects and then has ascribed the cause of these effects to one source of hormones (that from meat from treated animals). In light of the advice from the experts, the EC has failed on two accounts: it has not observed adverse effects that can be co-related to hormones; and even to the extent that it has observed such effects, it has not investigated the role of hormones writ large, preferring instead to focus on the single source of hormones.

Q25. To what extent do the three recent studies referred to by the European Communities confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones? Please also comment on the EC statement that one of the studies "was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, which means that the subjects should have been exposed to hormone-free meat in their diet. This may further imply that it cannot be excluded that the risk of cancer may be further increased if meat treated with hormones for animal growth promotion were to be consumed". [see paras. 145-148 of EC Rebuttal Submission (US case) and paras. 139-142 of EC Rebuttal

Submission (Canada case), footnote 97 in para. 147 of EC Rebuttal Submission (US case), and Exhibits EC-71, 72, 73]

97. Drs. Boisseau, Boobis and Guttenplan expressly deny that the three studies referred to by the EC confirm a risk to human health from exposure to hormone residues from meat from treated animals. Only Dr. Cogliano endorses the EC's attempt to use these studies as evidence of risk from consuming hormones from meat from treated animals, but he does so without any supporting evidence or analysis.

98. With respect to the study on zeranol[46], Drs. Boobis and Guttenplan both indicate that the study was based only on *in vitro* experiments and therefore cannot be extrapolated to human exposure. They find it particularly difficult to extrapolate to exposure from meat consumption since the dose used in the study was high, a point that even Dr. Cogliano acknowledges. In response to the observations of positive genotoxicity findings *in vitro*, Dr. Boobis notes that "genotoxicity by this mechanism [redox cycling] should exhibit a threshold and is also militated against in vivo by antioxidant defence systems and efficient repair of oxidant-damaged DNA."

99. With respect to the study on the relationship between intake of red meat and colorectal cancer,[47] Dr. Boisseau simply refers to his general scepticism of the ability of epidemiological studies to identify specific causal agents due to confounding factors. Dr. Boobis is even more specific in dismissing the relevance of this study, noting that its results are not new, that they are consistent across geographical area, and that even the authors point to possible explanations, such as the formation of mutagens during the cooking of meat and the generation of nitroso compounds. He notes that the study provides "little support for a contribution from hormones present in meat from their use as growth promoters … because the association is just as strong in regions where hormones are not used as where they are used".

100. Dr. Boobis is the only expert to make any detailed comments on the study of the relationship between hormone replacement therapy and the incidence of breast cancer.[48] He notes again that this study did not find any relationship that had not already been observed in the past, and that had not already been acknowledged by JECFA. The real issue, therefore, is not whether there is such a relationship, but whether that relationship has any relevance for the assessment of risk from the consumption of hormones in meat from treated animals. On this point, Dr. Boobis advises that it does not, because the "weight of evidence is such that the hormones cause cancer by a mechanism exhibiting a threshold" and the doses of hormones involved in this study were considerably higher than that found in meat from treated animals.

101. Ultimately, the experts' reactions to the specific quote from the EC (about the studies having been conducted after the ban) capture the overall response to the EC's use of these studies. Dr. Boisseau considers that this comment "expresses a concern but does not provide any scientific evidence supporting this concern", whereas Dr. Guttenplan considers that it "negates any relevance to the possible connection of hormone-treated meat consumption and cancer". Dr. Boobis considers that the only way the timing of the studies would matter would be if it were proven that there were risks from hormones from meat from treated animals, which Dr. Boobis confirms again has not been demonstrated. Dr. Boobis is more pointed in his criticism of the EC's suggestion that "it can not be excluded" that there is greater risk. He advises that since the same statement can be made in the absence of any study whatsoever of the risk from hormones, this statement is "not scientifically defensible".

[46] Exhibit EC-73.
[47] Exhibit EC-71.
[48] Exhibit EC-72.

102. These reactions highlight a tactic employed by the EC, namely, the manipulation of a genuine scientific interest in assessing the possible adverse effects arising from exposure to a substance in general (*i.e.*, hormones) to create specific and unjustified concern about possible adverse effects from one single and insignificant source of that substance in particular.

Q26. Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91]

103. As with their responses to the previous questions related to the potential of epidemiological studies, Drs. Boisseau, Boobis, Cogliano and Guttenplan all agree that the studies relied upon by the EC, in particular the epidemiological studies, do not identify a relationship between cancer and residues of hormones from meat from treated animals.

104. Many of the reasons they provide have already been discussed above, such as confounding factors, *etc*. The EC places considerable emphasis on statistics comparing breast and prostrate cancer rates between Europe, where hormones are banned for growth-promotion purposes, and North America, where they are not. Not surprisingly, while there may be some observable differences in rates between certain regions and ethnic groups, on the whole the rates are relatively similar. The experts agree that the differences that do exist are so slight as to be not statistically significant. To the extent that there are differences at all, Dr. Boobis cautions against inferring too much from geographical differences in cancer rates, because of what he calls an "ecological fallacy" (the belief that differences observed between groups will also be observed between individuals). More importantly, none of these studies relied upon by the EC included assessments of data on hormone intake, so even if the differences were significant (and they are not) no link can be made between these statistics and the consumption of meat from animals treated with the hormones at issue.

(b) Residue analysis

Q27. How do the residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue?

105. The experts who respond to this question (Drs. Boisseau and de Brabander) agree that since the chemical structures of the three synthetic hormones (zeranol, trenbolone acetate (TBA) and melengestrol acetate (MGA)) are different from the structure of the three natural hormones (oestradiol 17β, testosterone, progesterone), the residues of the synthetic hormones in the meat of treated cattle will be different from the residues in meat from cattle treated with natural hormones.

Q28. How do the hormones naturally present in animals, meat, or human beings differ from the residues in meat of the three natural hormones used for growth promotion purposes?

106. Dr. Boisseau and Dr. de Brabander address this question. Dr. Boisseau states:

> The definition of residues encompasses both the parent substance and all the metabolites derived from this parent substance. Therefore, in the case of the part of residues of the natural hormones which consists of parent substances, there is no difference between hormones naturally present in food producing animals, meat or

> human beings. Metabolites of these natural hormones existing in cattle and meat are, obviously, the same. To my knowledge, there is no scientific evidence showing that the main metabolites of the three natural hormones existing in cattle and humans are not similar.

107. For the sake of clarity, the Panel may wish to ask that Dr. Boisseau clarify whether the residues, both parent and metabolite, in meat from cattle treated with the three natural growth promoting hormones are the same as their respective endogenous natural hormones found in animals, meat or human beings.

108. Dr. de Brabander's opinion is much less clear. First he states that "there are no differences", then he qualifies his statement with references to unspecified "ongoing research". He states that "[t]he residues of the natural hormones in cattle are in the 17α form (inactive) while the use of 'natural' hormones used for growth promotion purposes may lead to residues in the β form (active form)." If Dr. de Brabander is suggesting that residues of natural hormones in untreated cattle do not occur in the β (active) form, he is contradicting his own answer to Question 31. There, he agrees that "residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle". Moreover, his position would be inconsistent with the detailed residue evidence reviewed by JECFA in its 1999 residue monograph. The monograph presents detailed data on hormone concentrations in various tissues, including muscle and fat, in untreated heifers and steers. Dr. de Brabander's suggestion in this regard simply does not withstand close scrutiny.[49]

Q29. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the synthetic hormones found in meat in their assessment of the risks from such residues? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? How do they compare with the MRLs set by Codex? [see paras. 165-176 of EC Rebuttal Submission (US case); pages 55-68 of the Opinion of the SCVPH of 30 April 1999 in US Exhibit 4, para. 144 of US First Submission, Exhibits US-6 and 7, footnote 46 of US Rebuttal Submission]

109. Dr. Boisseau confirms that the level of residues is typically taken into consideration at the third step of the risk assessment process, namely the exposure assessment, after the ADI has been established. The purpose of evaluating the level of residues in food is to ensure that dietary exposure to the substance does not exceed the ADI. Dr. Boisseau confirms that the SCVPH did not "conduct a quantitative assessment of the exposure of consumers to the residues of [synthetic] hormonal growth promoters including the determination of the levels of residues in food from treated animals, the impact of the non observance of good veterinary practices on these levels and the comparison between these levels and the MRLs set up by Codex".

110. Dr. de Brabander fails to directly answer the Panel's question. Instead, he appears to offer his own opinion regarding the inaccuracy of published concentrations of residues. Referring to Table 8 in the SCVPH 1999 Opinion[50], he indicates that residue levels for trenbolone are "extremely low…and serious doubts about their accuracy can be made." Table 8 is drawn in part from the extensive review of residue data contained in the JECFA Monograph to the 34th Meeting.[51] By quoting the JECFA data without qualification, the SCVPH does not appear to share Dr. de Brabander's concerns about the

[49] JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12 (Rome: FAO, 2000), at p. 38 (Exhibit CDA-17).

[50] 1999 SCVPH Opinion, Section 4.4.2, at p. 56 (Exhibit CDA-2).

[51] JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Thirty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food and Nutrition Paper, No. 41/2 (Rome: FAO, 1990), at pp. 88-100, in particular p. 96 (Exhibit CDA-38).

inaccuracy of the trenbolone residue data.[52] In any event, in contrast to the JECFA analysis, Dr. de Brabander fails to provide a single reference for his conclusion that "concentrations may seriously be underestimated."

111. Dr. de Brabander's statement that the MRLs set by Codex are high in relation to "modern analytical limits" is confusing. MRLs are a function of the ADI and are not set on the basis of detection methods, but toxicological data. As Dr. Boisseau states in response to Question 32, for control purposes, a validated analytical method need be only as sensitive as is necessary to detect residues at the established MRL. Thus, it makes little sense to assert that the MRLs are high unless there is evidence to suggest that the ADI is set too high. Moreover, Dr. de Brabander lists the MRL for MGA, an MRL that was recommended by JECFA as recently as February 2004 (62nd meeting). Dr. de Brabander appears to suggest that the analytical techniques used by JECFA in 2004 were not sufficiently "modern". However, his cursory conclusion is in stark contrast to the extensive evaluation of residue data conducted by JECFA.[53] In particular, recent residue data from studies using "modern" validated methods (HPLC-MS, GC-MS and LC-MS) were assessed in the JECFA Residue Monograph for the 58th Meeting.[54] All ten studies cited date from 1999 to 2002.

112. Lastly, Dr. de Brabander indicates that "[a]s demonstrated in several documents a major part of the hormones used are excreted through the faeces (for MGA ca. 75%)…" It would be helpful if Dr. de Brabander could provide citations for documents to which he refers. In addition, for completeness, it would be helpful if Dr. de Brabander could provide corresponding statistics in relation to excretion for all the hormones at issue, synthetic and natural.

Q30. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the three natural hormones in meat in their assessment of the risks from such residues? Is it possible to compare these to the ADIs recommended by JECFA in 1999? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? [see paras. 120-123 and 155-164 of EC Rebuttal Submission (US case), pages 33-54 of 1999 Opinion in Exhibit US-4, para. 144 of US First Submission, and 52nd JECFA Report in Exhibit US-5]

113. Both Dr. Boobis and Dr. Boisseau confirm that the SCVPH did not itself evaluate evidence of actual residue levels of the three natural hormones in its assessment of risks from such residues.[55] In addressing the impact of GVP on residue levels in meat, Dr. Boobis explains that, while the SCVPH considered potential exposure following inappropriate use scenarios, "these data are limited in the

[52] 1999 SCVPH Opinion, Section 4.4.2, at p. 56 (Exhibit CDA-2).

[53] See JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Sixty-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/16 (Rome: FAO, 2004) (Exhibit CDA-33); JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/14 (Rome: FAO, 2002) (Exhibit CDA-35); and JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/13 (Rome: FAO, 2000) (Exhibit CDA-37).

[54] JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/14 (Rome: FAO, 2002) (Exhibit CDA-35), pp. 56-59. All of the 10 studies cited by JECFA in this Monograph are from 1999-2002.

[55] Dr. Boobis, at p. 33. Dr. Boisseau refers back to his answer to Question 29, in which he concluded that the EC failed to "conduct a quantitative assessment of the exposure of consumers to the residues of [natural] hormonal growth promoters including the determination of the levels of residues in food from treated animals, the impact of the non observance of good veterinary practices on these levels and the comparison between these levels and the [ADI] set up by Codex."

absence of any information on the frequency of occurrence of such misuse in the use of the products in question." Moreover, he confirmed that "[i]t would have been possible to compare the SCVPHs estimates of exposure [in the misuse scenarios] with the ADIs derived by the JECFA but this was not done." Lastly, he concludes that the "ADI would have exceeded the exposure estimates for the three [natural] hormones." This advice supports the conclusion that the EC has not properly assessed the potential occurrence of adverse affects from the misuse of the natural hormones in question.

114. Unfortunately, Dr. de Brabander fails to directly answer the Panel's question. Instead, he refers to "old" data for residue concentrations and concludes without any analysis that their "accuracy could be doubted." Rather than responding directly to the Panel's question, he discusses, amongst other things, the potential environmental effects of hormone residue in excrement and the side-effects of testosterone spray used to enhance a woman's enjoyment of sex.

Q31. Please comment on the US statement that "concentrations of oestradiol 17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of oestradiol 17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." In your reply please take into account the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels" and the statement by the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered. [see paras. 51 and 144 of US First Submission and Exhibits US-6 and 7, para. 98 of EC Replies to Panel Questions, Exhibit EC-101, and para. 2.3.2.3 of the 1999 Report of SCVPH]

115. Dr. de Brabander offers qualified agreement with the US statement.

116. Both Drs. Boisseau and de Brabander indicate that meat consumption from pregnant heifers is exceptional. However, this conclusion is at odds with the evidence considered by the UK Sub-Group of the Veterinary Products Committee.[56] The Sub-Group analyzed the effect on exposure to oestradiol 17β in meat from the termination of the Over Thirty Months Scheme (OTMS) in the UK, a program that removes culled adult cows from the food chain. The Sub-Group concluded that "the removal of these pregnant cull cows to the food chain [as a result of the OTMS] has reduced the quantity of oestradiol in the food chain by 37% … which will be returned as the BSE controls are removed and the market returns to normal."[57] This is based on the assumption that 25% of slaughtered cows are in calf, at stages of pregnancy evenly distributed over the three trimesters.

117. In a different vein, Dr. Boisseau's response to this question also supports Canada's basic point that the EC is attempting to divorce the use of growth-promoting hormones from their appropriate context and, as a result, presents a distorted assessment of the risks associated with the use of growth-promoting hormones. He states:

> Even if, accepting the substance of the EC comment [meat consumption from pregnant heifers is exceptional], it is possible to limit the physiological range of

[56] UK, Sub-Group of the Veterinary Products Committee, *Executive summary and critical evaluation of the scientific reasoning and methods of argument adopted in the opinion of the Scientific Committee on Veterinary Measures Relating to Public Health which assessed the potential risks to human health from hormone residues in bovine meat and meat products*, October 1999 (Exhibits CDA-6, US-12).

[57] *Ibid*., at para. 56, pp. 19-20.

> oestradiol 17β and of progesterone in cattle, it has nevertheless to be recognized that (1) consumers are exposed to these two natural hormones through their consumption of meat and milk from the different non treated food producing animals and, mainly as least for women, through their endogenous production, (2) this exposure cannot be avoided. Therefore, the use of the concept of threshold in the risk assessment of the natural hormone residues is legitimate and the additional intake of residues of these natural hormones from the meat from treated cattle has to be considered in this context and not according to a theoretical "no additional intake of residues is acceptable".[emphasis added]

118. In essence, Dr. Boisseau advises that, in order appropriately to understand the risks associated with the use of growth-promoting hormones, one must view the exposure to these hormones in their overall context, including the wide exposure to natural hormones from other dietary sources and endogenous production of natural hormones. To posit that the risks arising from the use of HGPs are such that no threshold for acceptable intake can be established is simply irrational and scientifically unjustified.

Q32. Please comment on the conclusions of the EC risk assessment (Opinion of the SCVPH of April 2002) that ultra sensitive methods to detect residues of hormones in animal tissues have become available but need further validation. What is the significance of this with regard to identifying whether the natural hormones in meat are endogenously produced or are residues of hormones used for growth promotion purposes?

119. The SCVPH's statement concerning ultra-sensitive detection methods appears to relate its discussion of analytical techniques set out in Section 4.1.1 of its 2002 Opinion. In that section, the SCVPH acknowledges that the "low number of samples does not allow a qualified validation of typical characteristics such as sensitivity, specificity, accuracy and reproducibility (study 1, study 8)."[58] The experts who answered this question appear to agree on the importance of validating analytical methods.[59] Dr. Boisseau states that "validation must be carried out in compliance with well defined and internationally accepted criteria". These criteria include accuracy, precision, sensitivity, specificity, reproducibility, and reliability.[60]

120. In terms of the second part of the Panel's question, Dr. Boisseau explains that once an MRL has been established, the sensitivity of the validated analytical method need only be consistent with the values established by the MRLs. Analytical methods that are more sensitive, or "ultra sensitive," are redundant for control purposes.

Q33. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

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[58] EC, Health & Consumer Protection Directorate-General, *Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health on Review of previous SCVPH opinions of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products*, adopted April 10, 2002, Section 4.1.1, at p. 9 (Exhibit CDA-7). See also p. 21.

[59] Drs. Boisseau and de Brabander.

[60] JECFA, *Procedures for Recommending Maxium Residue Limits*, at p. 37 (Exhibit CDA-44).

121. Three experts respond to this question. JECFA also responds to the same question asked of the international bodies (Question 20). JECFA indicates that it can decide to re-evaluate previous assessments when it is made aware that there are new data which may be pertinent to the risk assessment of the substances in question. The claim by the EC in *EC – Hormones* that it had new evidence showing that oestradiol 17β was a direct acting genotoxic carcinogen appears to have promoted, at least in part, JECFA's 1999 re-evaluation. Moreover, JECFA indicates that new studies had also been published for the other hormones. This is consistent with the advice of Dr. Boisseau.

122. In terms of whether the residue data for the natural hormones used in 1999 were the same as those used in 1988, JECFA indicates that while most of the residue studies were the same, a few additional studies were reviewed. JECFA also states that it performed a more detailed review of the validity of the analytical methods used in the studies and used only data generated using valid methods.

123. JECFA also confirms that in the 1999 evaluation new toxicological and epidemiological data for the three natural hormones were evaluated, a position that is supported by Dr. Boobis. JECFA is quite specific as to the new information that was not available to it in 1988 but was available and considered by it in 1999.

124. In terms of whether the conclusions from the two evaluations differed, Dr. Boisseau confirms that in substance the conclusions remained the same. The risk assessment indicated a wide margin of safety for consumption of residues in meat from treated cattle. Hence, the establishment of numerical MRLs was not necessary to protect human health.[61]

125. As to the reasons for establishing ADIs for the three natural hormones in 1999, JECFA refers to "[t]he additional data reviewed and the need to establish and [*sic*] ADI as quantitative estimate for a safe oral intake".[62] This is consistent with Dr. Boobis' explanation that in the intervening years between the first and second JECFA evaluations, it became clear that exposure to natural hormones, albeit at levels much higher than that found in meat from treated cattle, could have adverse effects in humans. The implicit conclusion was that it was necessary to establish ADIs as benchmarks to ensure that exposure to these hormones through dietary sources did not cause adverse effects observed in other areas.

126. JECFA confirms that "the establishment of an ADI implies that there is a threshold of effect for such a compound, below which now [*sic*; read "no"] toxicological effects occur".[63] This conclusion is supported by both Dr. Boisseau and Dr. Boobis.

127. As to the reasons for CCRVDF's not having considered JECFA's more recent recommendations in respect of the natural hormones, JECFA's answer to Question 20 (to the international bodies) includes a direct quote from the 12th CCRVDF report, which states:

> Recognizing that this Committee had not requested the re-evaluation of these substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, the Committee decided not to consider these new recommendations.

128. As Dr. Boobis explains, the result is that Codex continues to list the three natural hormones with an indication that MRLs are "unnecessary" for tissues from cattle.

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[61] JECFA's answer to Question 20 (to the international bodies), at p. 18.
[62] *Ibid*.
[63] *Ibid*.

Q34. Please comment on the EC argument that the 1999 JECFA report based its findings on (a) outdated residues data and (b) not on evidence from residues in meat but on studies with experimental animals and on general studies of IARC. If the data were not new, did JECFA take this into account in its evaluation? What are the implications of using such data for the purpose of conducting a risk assessment? How reliable are extrapolations from animal studies to possible adverse effects on humans? How does this compare with the kind of data and studies used with respect to other veterinary drugs? [see para. 120 of EC Rebuttal Submission (US case), para. 102 of EC Rebuttal (Canada case)]

Outdated Residues Data

129. Dr. Boisseau confirms what is generally accepted within the scientific community: that scientific data do not deteriorate simply because of the passage of time. He concludes that "the quality and the number of the available data are more important than the dates at which these data have been produced." Dr. Boisseau also confirms that it is standard practice for JECFA to determine the quality and sufficiency of the data under consideration in its assessment of substances, as well as the validity of the analytical methods employed.[64]

130. In the specific case of the hormones at issue, Dr. Boisseau confirms that:

> JECFA has considered that the quality and the number of the available residue data were satisfactory and therefore the fact that these data were not new had no specific impact on its evaluation.

131. Thus, the EC's suggestion that old data are necessarily unreliable data is simply groundless. Obviously old data that have been generated using validated analytical methods are to be preferred over more recent data generated by unvalidated and widely ignored analytical techniques. At the end of the day, the expert advice supports Canada's position that sufficient scientific evidence exists to conduct a risk assessment for all six of the hormones at issue.

Type of Data and Extrapolations from Animal to Human

132. It should first be noted that the EC's statement in paragraph 102 of its Rebuttal Submission makes little sense. Studies with experimental animals are always *in vivo* and cannot by definition be *in vitro*. *In vitro* studies are studies that are conducted in an artificial environment outside the living organism.

133. To the extent that the EC's statement suggests that there is something unusual or inappropriate about making extensive use of studies with experimental animals and general studies by IARC, the experts' responses to this question demonstrate that such a suggestion is nonsense. Understandably, Dr. Boisseau expresses surprise with the EC's statements, stating:

> … it is the normal way for assessing the toxicological potential of a substance to take into consideration in vivo studies with experimental animals, in vitro studies and also reports already published by internationally recognized scientific organisations such as IARC.

134. Where human studies are not available, which is typically the case, for ethical reasons, risk assessors resort to these other studies out of necessity. Extrapolations from animal studies to humans

[64] For a description of JECFA's approach to data quality, see EHC-70, at pp. 22-23. ("JECFA has always judged studies on their merits, the main criteria being that the study was: (a) carried out with scientific rigour, and (b) reported in sufficient detail to enable comprehensive evaluation of the validity of the results.")

have been standard practice for many years and regularly applied by international and national agencies in the conduct of risk assessments for food additives and contaminants, as well as veterinary drugs. It should be emphasized however, that in the case of the natural hormones, JECFA made extensive use of data derived from human studies involving the three natural hormones, in addition to animal studies. Moreover, this statement is all the more surprising when one considers that the very type of studies that the EC appears to suggest are inappropriate are precisely the type of studies relied upon by the SCVPH.

135. As the experts confirm, the data and process used for assessing the safety of the hormones at issue are the same as those used for other veterinary drugs. JECFA has applied well-recognized procedures and principles in conducting its various risk assessments for the hormones at issue. Rather, the EC has strayed from internationally recognized techniques and methodologies.

Q35. Please comment on the European Communities claim that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. Is this correct? Have subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies? [see para. 171 of EC Rebuttal Submission (US case), para. 161 of EC Rebuttal Submission (Canada case), para. 55, including footnote 60 of US First Submission and Exhibits CDA-20, 33, 34, and 35]

136. Dr. Boisseau's answer to Question 34 also applies to this question, namely, that the quality and quantity of data are more important than the date upon which the data were generated.

137. While the studies referred to in the 2000 JECFA Report on MGA date back to the 1960s and 1970s[65], JECFA assessed these data to determine whether the quality and quantity were sufficient to conduct its risk assessment. As Dr. Boisseau concludes, "JECFA considered a wide series of toxicological studies in its assessment, used as end point a non hormonal effect dose by far more conservative than a NOAEL based on tumorigenic effect and adopted a 200 safety factor to derive an ADI from this NOAEL."

(c) Dose-response relationship

Q36. How would you describe a dose-response assessment? Is it, as suggested by Canada in para. 78 of its Rebuttal Submission, "widely, if not universally, accepted that adverse effects arising from hormonal activities are dose-dependent"? Is dose-response assessment a necessary component of hazard characterization? Or, is there an alternative approach which can replace the dose-response assessment. Is a dose-response assessment feasible/necessary for substances that are found to be genotoxic or to have genotoxic potential? [see para. 153 of EC Replies to Panel Questions, para. 200 of EC Rebuttal Submission (US case); paras. 143, 154, and 156 of US First Submission, paras. 70-74 of US Replies to Panel Questions, and paras. 34 and 37-40 of US Rebuttal Submission; paras. 76-82 of Canada Rebuttal Submission]

138. Two of the three experts who responded to this question (Drs. Boobis and Boisseau) confirm that a dose-response assessment is a necessary component of hazard characterization. While these experts also acknowledge that such an assessment may not be feasible or required for substances that are genotoxic *in vivo*, they both confirm that this exception is not absolute. Dr. Boisseau confirms that this exception only applies to xenobiotic substances (*i.e.*, those that are foreign to the human body) or to substances with "genotoxic potential" where it is thought that this potential can be expressed in *in vivo* conditions. At least for the natural hormones involved here, neither of these conditions is met such that a dose-response assessment should be skipped.

[65] Exhibit CDA-37.

139. Dr. Boobis similarly describes at least two general sets of circumstances in which a dose-response assessment would still be conducted on substances thought to have genotoxic potential. First, if the mechanism of action of the genotoxic effect was known, and it was of the type of mechanism that is known to exhibit a threshold (for example, substances with kinetic or dynamic causes, as well as those caused by reactive oxygen species), then a dose-response assessment is necessary. Second, if the mechanism of action of genotoxicity was known or assumed to be DNA-reactive, then this genotoxicity would need to be confirmed *in vivo* before it would be appropriate to dispense with a dose-response assessment. As we know from numerous sources, including the EC risk assessment itself, it has not been demonstrated that any of these six hormones have genotoxic potential *in vivo*. According to the experts, this requires that a dose-response assessment be conducted.

140. Dr. Cogliano's short response suggesting a dose-response may not be required tells only half the story. His comments seem to be limited to circumstances involving a "hazard-based approach", without explanation of when such an approach is or is not appropriate. A hazard-based approach simply identifies whether a substance is *capable* of causing an adverse effect under certain conditions, and not whether such adverse effect would actually occur at given doses. This corresponds only to the "hazard identification" stage of a risk assessment (*i.e.*, whether a substance can cause an adverse effect) and disregards the hazard characterization stage, which includes an assessment of the dose required to provoke the identified hazard (*i.e.*, dose-response assessment).[66] Quite apart from the explanation from Dr. Boobis that a "hazard-based approach" is not appropriate for these hormones, it would also be inconsistent with obligations under the *SPS Agreement* that a substance be evaluated for the potential for occurrence of an adverse effect.

141. Dr. Cogliano's view that a dose-response assessment is optional is inconsistent with his later view that it is "widely accepted that adverse effects arising from hormonal activities depend on the dose".

Q37. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

142. Drs. Boisseau and Boobis confirm Canada's statement that international techniques require that a dose-response assessment always be conducted as part of an assessment of the risk from chemical substances such as the six hormones. Dr. Boisseau indicates that it would not be possible to establish an ADI, and Dr. Boobis indicates that it would not be possible to recommend MRLs, in the absence of a dose-response assessment. These opinions are confirmed by JECFA in its response to Question 8 to the international bodies. In light of the universally held view that the adverse effects of hormones are dose-dependent, these answers are not at all surprising given the purpose of the dose-response assessment of determining as closely as possible the level of dose at which there is no response (*i.e.*, the NOAEL).

(d) Sensitive populations

Q38. Please describe the range of physiological (or background) levels of the sex hormones in humans and identify the variations in these levels on the basis of age, sex group, and physiological stages.

143. In presenting various figures for background levels of sex hormones of different age groups in response to this question, Dr. Boisseau raises concerns, as many others have done, about the reliance

[66] See Canada's comments on the experts' responses to Question 11.

by the EC on a new "ultrasensitive bioassay" (also referred to as the Klein assay). In light of the SCVPH's decision to revise downward by 100-fold the estimated physiological level of hormones in pre-pubertal boys and girls, and the significance of the conclusions it draws as a result, Dr. Boisseau raises the important point about whether this assay has been validated. More detailed discussion of the flaws of this methodology follow in Canada's comments on the experts' responses to Question 40.

Q39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol 17β and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the populations which have been identified as particularly sensitive such as prepubertal children" [see para. 147 of the EC Replies to Panel Questions]

144. In his reply to this question, Dr. Boisseau confirms that the EC has failed to compare quantitatively the exposure to oestradiol 17β from meat from treated animals to that from meat from non-treated animals and other sources of oestradiol 17β. Without having conducted such a comparison, the SCVPH is unable to claim that such exposure is "excess", nor that, even if it is "excess", the amount of the excess would be sufficient to "present a potential risk to public health".

145. While Dr. Sippell offers the view that the EC's claim is supported, the evidence he refers to largely involves the controversial, and yet-to-be validated, methodology for measuring background levels of oestradiol 17β (*i.e.*, the Klein assay). Quite apart from the fact that serious concerns have been expressed about the validity of this methodology,[67] the use of the methodology does not, on its own, support the conclusion that exposure to oestradiol 17β residues from treated meat amounts to "excess exposure", nor that it "presents a potential risk to public health". Almost all the studies cited by Dr. Sippell apply to oestrogen in general, and not to residues of oestradiol 17β consumed via meat from treated animals.

146. Therefore, when Dr. Sippell refers to "elevated estrogen levels", he provides no evidence whatsoever that such levels are achieved from the consumption of residues of hormones from meat from treated animals. On the contrary, to the extent that his greatest concern appears to be for exposure to oestradiol 17β during "early life" (*i.e.*, pre- and post-natal periods), Dr. Sippell provides no evidence for, nor even a plausible explanation of, exposure at this age to residues from meat products. Certainly a foetus/infant could be exposed via the mother, but since late pregnancy and early *post partum* are the periods of a woman's life where the natural oestrogen level is at its most elevated, the proportion of oestrogen exposure of the foetus/infant that would come from the consumption by the mother of meat from treated animals would be trivial.

147. Moreover, a review of the full context of the quote cited in the question[68] reveals that it is based on conclusions that the experts have contested elsewhere in their replies. Citing disputed findings that metabolites of oestradiol 17β have "genotoxic potential", the SCVPH concludes that oestradiol 17β is both a tumour initiator as well tumour promoter. It then suggests that this conclusion is confirmed by epidemiological data and IARC's classification of oestrogen as a human carcinogen. On the basis of these findings, the SCVPH further concludes that "any excess exposure… presents a potential risk to public health". [69] However, in establishing the adverse effect threshold as "any excess exposure", the SCVPH offered no confirmed evidence of genotoxicity of the substances, nor any scientific support for its suggestion of a link between epidemiological data and its conclusions. The result is that the quote from the SCVPH's opinion is no more than speculation based on tenuous links drawn between unsupported conclusions.

[67] See Canada's comments on Question 40.
[68] 1999 SCVPH Opinion, at pp. 74-75 (Exhibit CDA-2).
[69] *Ibid*., at p. 74.

Q40. The European Communities states that "the levels of endogenous production of the hormones by prepubertal children is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship..." Please comment on the methodology used by the SCVPH to support the conclusion that hormone levels are lower than previously thought, and in particular comment on the validity of these methodologies and their conclusions. Would your conclusions have been the same at the time of adoption of the Directive in September 2003?

148. Drs. Boisseau and Boobis both share concerns about the methodology (an "ultrasensitive" recombinant cell bioassay (RCBA) developed by Klein and others[70]) that generated the underpinning the conclusion that endogenous levels of hormones in pre-pubertal children are lower than previously thought. Dr. Boisseau's concerns about the absence of validation of this methodology are reflected in his answer to Question 38.

149. Dr. Boobis echoes these concerns in a very comprehensive review of the issues surrounding this controversial methodology. While he acknowledges that endogenous levels may be lower than previously thought, Dr. Boobis expresses grave doubts that this is by the "orders of magnitude" suggested by the SCVPH, repeating Dr. Boisseau's concern when he says that the "reliability of the Klein *et al.* assay has yet to be determined". He points to a number of contradictory results in the use of this assay, including from the original inventors themselves, that at the very least suggests that it has not been adequately validated for use in a risk assessment.

150. The concerns highlighted by the experts about the SCVPH's use of this methodology have been consistently cited by others as one of the flaws in the analysis of the SCVPH. For example, the UK Sub-Group Report early on expressed the concern that the Klein assays have not been appropriately validated. It expressed:

> … concerns about the reliability of this analytical approach, which has been very little used in peer-reviewed publications other than by the originators of the assay, despite its initial publication in 1994. These concerns throw doubt upon the values derived by Klein *et al.* and therefore also on the conclusions of the [SCVPH] opinion.[71]

151. Not only does the SCVPH fail to point out the obvious problems with the validity of the Klein data, but it ends up comparing apples with oranges. The 1999 SCVPH Opinion recognizes that "perhaps the hormone residues in beef, which are also low and which have also been determined by Radio Immune Assays (RIA) are equally variable and over representative of the actual hormone concentrations."[72] Thereafter, without acknowledging that it is using two different analytical techniques, the SCVPH goes on to compare concentrations of oestradiol in beef using RIA with concentrations in plasma using the Klein assay. As the UK Sub-Group Report concluded, "[t]his is inappropriate and may lead to a biased inappropriate perspective."[73]

152. Most importantly, even the 1999 SCVPH Opinion calls the data produced by Klein *et al.* "experimental evidence", calling the data "insufficient" to form the basis of a sound risk assessment.[74] A few years later, the SCVPH itself concluded in its 2002 opinion that "[t]he obtained results suggest

[70] *Ibid.*, at pp. 30 and 38.
[71] UK Sub-Group Report, at pp. 26-28 (Exhibit CDA-6).
[72] 1999 SCVPH Opinion, at p. 30 (Exhibit CDA-2).
[73] UK Sub-Group Report, at para. 96, p. 28 (Exhibit CDA-6).
[74] 1999 SCVPH Opinion, at pp. 38-9 (Exhibit CDA-2).

that the use of recombinant yeast and rainbow trout hepatocytes to detect oestrogenic compounds is not justified in view of their lack of sensitivity."[75]).

153. Contrary to the concerns expressed by at least two of his colleagues, Dr. Sippell seems to believe the recombinant yeast bioassay (RCBA) methodology constitutes a "quantum leap" in assay methodology. In support of this claim, Dr. Sippell cites a later study (Paris *et al.*, 2002) to suggest that the Klein RCBA has been validated. Interestingly, the research by Paris *et al.* was also cited by Dr. Boobis in support of his opinion that the Klein RCBA had not been validated by subsequent research because the research by Paris *et al.*, which in Dr. Boobis' mind is more credible, demonstrated that the Klein RCBA overestimated background oestrogen levels by up to 18 times. The Paris *et al.* results in fact were closer to the original data used by JECFA based on the RIA methodology. In light of these discrepancies, the Panel may wish to ask Dr. Sippell to clarify why he believes the Paris *et al.* results validate the 1994 Klein results.

154. Dr. Sippell makes another ambiguous observation in his advice when he states that "the complexity of the [Klein] RCBA so far prevents its wider use for routine measurements in small serum samples from infants and prepubertal children". Canada understands this to be confirmation that there are very little reliable data related to the use of RCBA.

Q41. Why would individuals with the lowest endogenous hormone levels be at greatest risk? How would the risks for these individuals arising from hormones naturally present in meat differ from the risks arising from the residues of hormone growth promoters?

155. Drs. Boisseau and Boobis agree that although individuals with the lowest endogenous hormone levels are at the greatest risk from any adverse effects that might result from exposure to hormones, the exposure to hormones via meat from treated animals would not result in any change in the effect that would be expected from hormones from meat from non-treated animals, or any other exogenous source for that matter.

156. Dr. Sippell suggests that the risks would be different, but he bases his assessment of "risk" on what he calls a "new threshold", which appears to be based on the results from the Klein assay. However, as the experts have advised in response to previous questions, this assay has not been validated sufficiently to support the kinds of conclusions that Dr. Sippell makes.

Q42. To what extent, in your view, has JECFA taken into account the particular situation of sensitive populations, in particular prepubertal children, in its risk assessments with respect to oestradiol 17β? Please compare the original data concerning endogenous production of natural hormones by prepubertal children upon which JECFA based its assessment and those used by the European Communities in its risk assessment. In your view, does the scientific material referred to by the European Communities require a revision of the Codex recommendation with respect to oestradiol 17β?

157. Drs. Boisseau and Boobis both acknowledge the many ways in which JECFA takes into account the situation of sensitive populations. They point in particular to the use by JECFA in establishing the ADI for oestradiol 17β of an additional safety factor of 10 specifically for sensitive populations, in addition to the initial safety factor of 10 for variation between individuals. The resulting safety factor of 100 makes for a very conservative assessment of safe exposure. Dr. Boisseau confirms that the safety factors for some of the other hormones were even greater. Moreover, Dr. Boisseau highlights two additional safety factors: first, that the estimated exposure to the natural hormones from meat from treated animals amounts to a very small proportion of the overall exposure from all sources, and, second, the fact that the bioavailability of the natural hormones is quite low.

[75] 2002 SCVPH Opinion, at p. 9 (Exhibit CDA-7).

The approach of JECFA builds in significant safety margins to take into account the situation of sensitive populations.

158. Only Dr. Sippell expresses concern about whether JECFA's analysis adequately takes into account the situation of sensitive populations, but his concern is based on estimates of endogenous levels in these populations that have been generated by the Klein RCBA. As discussed above, however, this methodology has not been adequately validated, and the original results obtained by Klein have not been reproduced by others. In light of more credible measurements of endogenous levels of hormones, Dr. Boobis indicates in his answer to Question 40 that exposure up to the ADI established by JECFA would still be safe for sensitive populations. Nothing in Dr. Sippell's comments (other than a non-validated methodology) contradicts the analysis conducted by Dr. Boobis.

159. Both Drs. Boisseau and Boobis indicate that the scientific material referred to by the EC does not require a revision of the Codex recommendation with respect to oestradiol 17β.

(e) Bioavailability

Q43. Please define bioavailability, comment on the significance of bioavailability to assessments of risk, and on the degree of bioavailabilitiy of the residues of the hormones at issue when consumed in meat, taking into account parties' differing views on this matter. [see paras. 123-124 of EC Rebuttal Submission (US case), paras. 105-106 of EC Rebuttal Submission (Canada case), paras. 100, 155-159 of the EC Replies to Panel Questions, paras. 32 and 41-42 of US Rebuttal Submission, paras. 69, 71, 88-89 and 146 of US First Submission, and para. 134 of Canada Rebuttal Submission]

160. The experts generally agree that bioavailability refers to the fraction of the substance that is available for systemic circulation. It is normally estimated by comparing the availability of a substance after oral administration with the availability of a substance after intravenous administration (which is assumed to be 100% bioavailable). The experts also agree that only the bioavailable portion of the substance at issue can produce an adverse effect. As a consequence, only that portion of the substance that is bioavailable will be significant for risk assessment purposes.

161. Dr. Boisseau and Dr. Boobis confirm that the natural hormones are either inactive orally or have low bioavailability (between 5% to 10%). These conclusions are supported by both JECFA[76] and CVMP.[77] The JECFA analysis is based on a review of the scientific literature on the absorption, distribution and excretion of oestradiol 17β set out in the Toxicological Monograph for the natural hormones prepared for JECFA's 52nd meeting.[78]

162. Dr. Guttenplan indicates that the "bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account[])." He further indicates that the SCVPH in its 1999 and 2002 opinions questions the sufficiency and accuracy of the data relied upon

[76] See JECFA, 52nd Report, at p. 58. (Exhibit CDA-16). ("In general, oestradiol-17β is inactive when given orally because it is inactivated in the gastrointestinal tract and liver".)

[77] European Medicines Agency, Committee for Veterinary Medicinal Products, *Report of the CVMP on the Safety Evaluation of Steroidal Sex Hormones in particular for 17β-Oestradiol, Progesterone, Altrenogest, Flugestone acetate and Norgestomet in the Light of New Data/Information made available by the European Commission*, EMEA/CVMP/885/99, December 1999, at p. 2 (Exhibit CDA-5). ("[T]he bioavailability of 17β-oestradiol esters after oral administration is low (3% as unchanged 17β-oestradiol), but it might be higher if estron, an estrogenic metabolite, is included".)

[78] See JECFA, *Toxicological evaluation of certain veterinary drug residues in food*: *prepared by the Fifty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Food Additives Series No. 43, (Geneva: WHO, 2000), Section 1.2.1 Absorption, distribution and excretion, at p. 45 (Exhibit CDA-11).

by JECFA. However, Dr. Boobis places the concept of bioavailability, and by extension the SCVPH analysis, in its proper context. He states:

> However, low bioavailability does not necessarily increase the margin of safety (the ratio of ADI to actual exposure). This is because the effects of concern are usually determined following exposure by the route of interest, in this case oral. Hence, the ADI represents a "bioavailability adjusted" dose, just as the TMDI does. The consequence of this is that anything that increases bioavailability will reduce the margin of safety whilst anything that reduces bioavailability will increase the margin of safety. In the case of the natural hormones, changes in bioavailability are likely to be a consequence of changes in the enzymes of metabolism in the liver and/or small intestine.

163. Thus, as the ADI is a "bioavailability adjusted" dose, for the purposes of establishing the ADI, it matters not that the estimated bioavailability of the substance is later revised. The ADI is based on the dose that represents the NOAEL, together with appropriate safety factors. Thus, even if the SCVPH is correct that the bioavailability of the hormones at issue is higher than previously estimated, a conclusion that Canada contests, this has no impact on the ADI. The ADI could be called in question if, for instance, studies demonstrate that the bioavailability of oestradiol 17β in residues in meat from treated cattle was higher than the bioavailability of the fine-particle oestradiol 17β used in the studies that formed the basis of the ADI. However, the EC has presented no evidence to this effect. Indeed, the evidence points in the opposite direction.

(f) Good veterinary practice (GVP)

Q44. Please define "good veterinary practice" (GVP) and/or "good practice in the use of veterinary drugs" (GPVD). What are the relevant Codex standards, guidelines or recommendations relating to GVP/GPVD? Please comment on the statement by the European Communities that the definition of the GPVD is "circular and hence problematic." [see para. 88 of the EC Replies to Panel Questions]

164. Two experts, Dr. Boisseau and Dr. de Brabander, answer this question. Codex also answers a similar question posed to the international bodies (Question 15). The Codex definition of GPVD, with which both experts agree, is as follows:

> Good Practice in the Use of Veterinary Drugs (GPVD) is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

165. In terms of Codex standards, guidelines and recommendations, Codex and Dr. de Brabander identify the Codex *Recommended International Code of Practice for Control of the Use of Veterinary Drugs (Codex Recommendations)*,[79] although Dr. de Brabander does so only in passing. Instead of discussing the *Codex Recommendations*, Dr. de Brabander extensively quotes from what appears to be a code of ethics and principles of conduct for the Federation of Veterinarians of Europe (FVE). Two points need to be made. First, the FVE code is not an international standard, guideline or recommendation. Second, a code governing ethical conduct is of limited relevance to risk assessments of veterinary drug residues in meat.

166. In contrast to the FVE, the *Codex Recommendations* addresses in detail such issues relating to the use of veterinary drugs as requirements for distribution, transport, and storage (*e.g.*, temperature,

[79] Codex, *Recommended International Code of Practice for Control of the Use of Veterinary Drugs (Codex Recommendations)*, CAC/RCP 38 (Exhibit CDA-47).

humidity, light, *etc*.); requirements on handling and administration (*e.g.*, dose, method of use); withdrawal periods; disposal; and record keeping. Notably, the *Codex Recommendations* do not suggest that all veterinary drugs must be administered by a veterinarian:

> [w]hen the administration of a medicine is not under direct veterinary supervision, it is therefore essential that, after the diagnosis, clear instructions should be provided on dose and methods of use, taking account of the competence of the user performing the work and ensuring that the correct calculation of, and the importance of adhering to, withdrawal periods is fully understood.[80]

167. Regrettably, neither expert discusses the detailed provisions of the *Codex Recommendations* or whether this document sheds light on the EC's claim that GVP is "somewhat circular and hence problematic." Canada shares Dr. Boisseau's concern that the EC's comment is less than clear. This concern may flow from the fact that the EC appears to be questioning a well recognized international practice, employed by its own agencies.[81] He posits that the EC means that the conditions of use of the veterinary drug may differ in a very significant way from one country to another. Here, Dr. Boisseau's answer to Question 45 is relevant.

168. Dr. Boisseau states that JECFA and other national authorities conduct risk assessments of veterinary drugs using studies in which the drug under review has been administered according to officially approved conditions of use (*i.e.*, labelled instructions). Thus, he suggests that adherence to GPVD is intricately linked to compliance with approved conditions of use (*e.g.*, storage, dose and method of use, withdrawal periods etc.).

169. The EC suggests that the circularity arises because "GVP is … dependent upon what national authorities consider appropriate". This only becomes problematic if the conditions of use that underlie the studies relied upon by JECFA are more stringent than approved conditions of use at the national level. Consequently, it would be helpful if the experts could clarify whether the approved conditions of use in Canada for the hormones in question differ from the conditions of use underlying the studies that JECFA used to assess the safety of these hormones.

Q45. In conducting a risk assessment of specific veterinary drugs, what assumptions are made concerning GVP, if any? How, if at all, are risks that might arise from the failure to follow good veterinary practice in the administration of veterinary drugs addressed?

170. Both Dr. Boisseau and Dr. de Brabander indicate that in conducting a risk assessment it is assumed that GVP is followed.[82] Dr. Boisseau explains in greater detail that JECFA and other national authorities conduct risk assessments of veterinary drugs using studies in which the drug under review has been administered according to officially approved conditions of use. As discussed above, for the most part, use in accordance with GPVD means use in accordance with the approved conditions of use (*e.g.*, storage, transport, dose, method of use, withdrawal period).

171. As regards the second part of the Panel's question, Dr. Boisseau indicates that it is very difficult for risk assessors to identify all possible permutations of misuse and abuse. In terms of the risks that might arise from the failure to follow GPVD, Dr. Boisseau states:

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[80] *Codex Recommendations*, at para. 5, p. 1.

[81] In this regard, see Dr. Boobis' answer to Question 46, in which he states "appropriate residues studies are those obtained after the normal use of the hormones, i.e. in accordance with GVP. This is the policy of all agencies and organisations involved in such activities (*EEC, 1990; EMEA, 2005; FAO, 2006*)."

[82] In the light of the answers to Question 44, Canada assumes that, when the Panel refers to GVP, it is actually referring to "good practice in the use of veterinary drugs" (GPVD).

> It would not be appropriate also because it would not be ethical for the case where such data, being available, would lead to the conclusion of the risk assessment that, given a possibly wide margin of safety for a veterinary drug under review, the excess intake of residues associated with these misuses/abuses does not raise any problem of public health.

172. Canada requests that Dr. Boisseau clarify whether he is suggesting that, with respect to the growth-promoting hormones at issue, such a wide margin of safety has been incorporated into the risk assessment that any misuse and abuse is unlikely to give rise to adverse effects for human health?

173. Dr. de Brabander fails to respond to the Panel's actual question.

Q46. To what extent were risks from misuse or abuse assessed by JECFA in its evaluation of the hormones at issue? In terms of the three synthetic hormones at issue, how is GVP relevant to the establishment of MRLs by JECFA?

174. Drs. Boobis, Boisseau and de Brabander respond to this question. Dr. Boisseau cites his answer to Question 45, implying he is of the view that the risks of misuse and abuse are not typically assessed by risk assessors such as JECFA. However, Dr. Boobis confirms that in several instances JECFA did consider the risks of misuse of some of the hormone growth promotants at issue, namely, zeranol and MGA.

175. Dr. Boobis also states that the point at which misuse and abuse is relevant in the risk assessment is at the risk characterization stage, during which potential exposure is compared with the ADI. He also states that, where appropriate, one could consider other potential exposure scenarios, such as the misuse and abuse of the substance in question.

176. Drs. Boobis and Boisseau appear of the view that it is not for JECFA to monitor compliance with GVP. Dr. Boisseau's answer to Question 45 above, is supported by Dr. Boobis' response to Question 62 where he states that:

> [misuse and abuse] cannot be used as the basis for establishing MRLs. This is because whilst use according to GVP can be foreseen and regulated, it is not possible or appropriate to regulate any conceivable misuse or abuse, whether actual or hypothetical. Normally, the risk management strategy to deal with this is to ensure adequate surveillance of residues and to put in place a system of penalties for violation. This is the situation for veterinary drugs in all regions where they are subject to market authorisation, including the EU and the USA.

177. Therefore, to the extent that the EC is suggesting that JECFA's risk assessment is somehow flawed because it failed to assess potential misuse and abuse, the EC is fundamentally misconstruing JECFA's role.

178. Dr. de Brabander's answer is confusing and difficult to follow. First, he suggests that JECFA "denied" that there was misuse and abuse. Canada has carefully reviewed JECFA's reports and can find no example of JECFA "denying" such a possibility. In the light of the responses of the other experts, the Panel may wish to ask Dr. de Brabander to support this allegation. Second, he appears to draw illogical conclusions about the relationship between misuse and abuse and the establishment of MRLs. He states:

> If other substances (like zilpaterol or ZMA etc …) or uncorrect [*sic*] use of implants are used the principle of the establishment of MRLs by JECFA is certainly unvalid [*sic*]

179. As Drs. Boobis and Boisseau explain, MRLs are established on the basis of the normal use of hormones, *i.e.*, in accordance with GVP, and are set independently of potential compliance issues. In the light of this evidence, Dr. de Brabander's conclusion is questionable, to say the least.

Q47. How significant are any differences in GVP in the European Communities, the United States, and Canada? Does the EC risk assessment take into account relevant control mechanisms with respect to GVP in place in the United States and/or Canada? If so, what are their conclusions?

180. Drs. Boisseau and de Brabander respond to this question. Dr. Boisseau, although acknowledging that he did not think that he was in a position to answer this question, indicates that in his view the main problem for the EC is that HGPs in North America are sold over the counter without veterinary supervision. He further states that "it is not possible to say that the European Communities took into account relevant control mechanisms with respect to GVPs in place in the USA and/or Canada" in its risk assessment.

181. On the other hand, in answering this question, Dr. de Brabander appears again to confuse concepts by suggesting that the very use of growth-promoting hormones is contrary to the principles of GVP. However, as the *Codex Recommendations* reveals, GVP establishes principles governing the use of veterinary drugs, but does not prescribe which substances can be used and for what purpose.

182. As to relevant control mechanisms, Dr. de Brabander again fails to answer the Panel's question and instead postulates that "any control mechanism, that is only based on audits and paper work will not prevent farmers to use either uncorrect [*sic*] use of legal production aids either the use of other illegal growth promotors which are readily available in the US and Canada through the internet." Aside from the fact that Dr. de Brabander is straying from his area of expertise, the only evidence presented to support his assertion is a warning issued by Health Canada concerning athletic performance-enhancing products containing illegal anabolic steroids.[83] Although it is less than clear, Dr. de Brabander appears to imply that because anabolic steroids are used illegally in performance enhancing products in Canada, control mechanisms short of a complete ban would not prevent the misuse and abuse of HGPs. This logic is deeply flawed. A warning issued by Health Canada to protect Canadians from illegal anabolic steroids in bodybuilding drugs is hardly credible evidence of the existence or extent of the misuse and abuse of HGPs or an evaluation of relevant control mechanism.

183. Moreover, the illegal use of anabolic steroids by athletes has been a world-wide problem for decades. Much of the internet trade in illegal anabolic steroids originates in Europe, where controls over the distribution of these products are more lax.[84] The implication of Dr. de Brabander's logic is that, because these products are available in Europe through the internet, European farmers are misusing anabolic steroids in the husbandry of cattle.

Q48. To what extent does the scientific evidence referred to by the European Communities assess risks to human health from residues of misplaced implants or improper administration, i.e. when administered differently than indicated on the label of the manufacturer or contrary

[83] Health Canada, Advisory, *Health Canada advises consumers not to use unauthorized products containing anabolic steroids*, April 21, 2006; online at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_17_e.html.

[84] US Drug Enforcement Agency, *Anabolic Steroids, A Dangerous and Illegal Way to Seek Athletic Dominance and a Better Appearance*, "For purposes of illegal use there are several sources; the most common illegal source is from smuggling steroids into the United States from other countries such as Mexico and European countries. Smuggling from these areas is easier because a prescription is not required for the purchase of steroids. Less often steroids found in the illicit market are diverted from legitimate sources (e.g. thefts or inappropriate prescribing) or produced in clandestine laboratories"; online at: http://www.deadiversion.usdoj.gov/pubs/brochures/steroids/public/public.pdf.

to GVP, of any of the six hormones? Would your reply have been different at the time of adoption of the EC Directive in September 2003? What are the potential hazards, if any, to human health of the use of large quantities, or doses higher than recommended, of any of the six hormones in dispute?

184. Although Drs. Boisseau, Boobis and de Brabander all provide answers, only the first two respond to the question posed by the Panel in a comprehensive fashion. These experts agree that the EC failed to assess risks to human health from residues of misplaced implants or improper administration. Dr. Boobis states directly that:

> There was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies. Indeed, the SCVPH (2002) simply noted that "Therefore, these data have to be considered in any quantitative exposure assessment exercise", without undertaking such an exercise.

185. For his part, Dr. Boisseau notes that the EC:

> … is right to state that, in case of these different misuses/abuses, the exposure of consumers may be totally different. Once again, this situation is not specific to hormones as it applies also to all the veterinary drugs already assessed by JECFA, EU, USA or anywhere else in the world.

186. These responses support Canada's explanation that the EC has failed to evaluate the potential risks to human health from the misuse or abuse of the growth-promoting hormones at issue.[85] The EC has simply identified the possibility that misuse or abuse could occur without having evaluated its frequency or the potential risk to human health in the event it occurs. As Dr. Boobis states:

> In my view, the potential hazards to the use of large quantities of the six hormones in dispute are those dependent on their endocrine activity, including cancer in hormonally responsive tissues. However, I should stress that this is their potential hazard. The potential risk, i.e. the probability that effects would occur, would depend on a number of factors. These include the magnitude of the exposure, the duration of the exposure and the life stage of the exposed individual. From the range of exposures likely from anticipated misuse or abuse the risks are likely to be very low.

187. In his response to Question 62, reviewing the EC's additional research conducted since 1997, Dr. Boobis further states:

> Taking account of all of these factors, the data generated by the EU research in question do not provide any indication that it is not possible to conduct a risk assessment of the hormones used as growth promoters. Nor do they provide any indication that even such misuse and abuse as investigated gives rise to undue risk from the resultant residues, as intake would only very rarely exceed the ADI and then only on a rare occasion. [86]

188. As Dr. Boisseau notes, the misuse and abuse of a substance could lead to exposure scenarios different from those contemplated in establishing an MRL. This applies to any veterinary drug, or indeed any substance for which an MRL is established. If it were sufficient for a WTO Member simply to raise the possibility, without any evaluation, of misuse and abuse as a justification for a ban

[85] Canada Rebuttal Submission, at paras. 107-111.
[86] Dr. Boobis, at p. 52.

on a substance, the obligation in Article 5.1 of the *SPS Agreement* to base an SPS measure on a risk assessment would be rendered illusory, and the work of international scientific risk assessment bodies, such as JECFA or the Joint Management Pesticide Committee, could be largely irrelevant. Mere assertions that misuse and abuse may occur without any evaluation of the factors outlined by Dr. Boobis on page 52 of his answers do not satisfy the requirements of a risk assessment as defined by the *SPS Agreement*.

Q49. What analytical methods, or other technical means, for residue detection in tissues exist to control the use of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice? What tools are available to control the use by farmers of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice?

189. Only Dr. de Brabander responds to this question. He indicates that:

> There are a large number of analytical methods available to control the use of the six hormones in dispute for growth promotion purposes. New methods are regularly presented in international conferences and in the open literature. In Europe a system of community reference (CRL) and national reference laboratories (NRL) is installed so that the analysis carried out by the field laboratories are kept up to the standards of the moment. If necessary I can provide the panel with a large number of methods but I don't think that is the purpose.

190. As it would be helpful to understanding the issues in dispute, the Panel may wish to ask Dr. de Brabander for a complete listing of available analytical methods to detect residues in meat and meat products for each of the hormones at issue as well as a complete description of the CRL and NRL networks to which he refers.

Q50. Are there other measures available to the European Communities (other than a complete ban) which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

191. Both Drs. Boisseau and de Brabander respond to this question. Dr. Boisseau makes a number of suggestions for addressing human health concerns arising from the failure by the exporting country to ensure compliance with GVP. He notes that a "[b]an is the last possible measure if all the other options have failed or have been proved ineffective."

192. In contrast, Dr. de Brabander states that there are no measures possible other than a complete ban that could address the risks arising from misuse and abuse. This remark appears inconsistent with his earlier statement in response to Question 49 that "[t]here are a large number of analytical methods available to control the use of the six hormones in dispute for growth promotion purposes."

Q51. Does the material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada call into question the potential applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada?

193. Both Drs. Boisseau and de Brabander respond to this question. Dr. Boisseau refers back to his answers to Questions 45 and 48, implying that, in his view, the misuse and abuse of hormones used for growth promotion do not call into question the potential applicability of Codex standards. Dr. Boisseau earlier commented that the establishment of ADIs and MRLs are based on an

assumption that GVP will be followed. Thus, in the unlikely event that GVP is not followed, the applicability of Codex standards is not put into doubt. Misuse or abuse may cause the residues of the substance in question to exceed the established MRL and may lead to exposure to the substance in excess of the established ADI, but it does not imply that the Codex standard is any less applicable. Questions of compliance with an MRL differ conceptually from whether the MRL is valid or applicable.

194. Unlike Dr. Boisseau, Dr. de Brabander appears to confuse the applicability of a Codex standard with the consequences of misuse and abuse. Then, he refers to "older" experiments upon which the ADIs and MRLs were based and suggests that "scientific knowledge on residues, their link with animal welfare and the impact on the environment has increased considerably." With respect, it is somewhat difficult to follow Dr. de Brabander's reasoning in this regard and it is less than clear how Dr. de Brabander's response addresses the Panel's question concerning misuse and abuse. To the extent that Dr. de Brabander suggests that the experiments on which the Codex ADI and MRL are based were "old" and no longer valid, he appears to be answering Question 34, on which Canada has already commented. Moreover, Dr. de Brabander's reference to his own study of the formation of boldenone has no bearing on the issue of misuse and abuse.

(g) Other

Q52. Do the risk assessment of the European Communities or any other scientific materials referred to by the European Communities demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes? If yes, why? If not, what kind of evidence would be required to demonstrate such potential adverse affects? Would your response have been different at the time of adoption of the Directive in September 2003?

195. Drs. Boisseau and Boobis both agree with Canada that the scientific evidence relied upon by the EC does not demonstrate that there are adverse effects from the consumption of residues of hormones through meat from treated animals. Dr. Boisseau states that the EC did not carry out a risk assessment, but, rather, simply "provided scientific data and hypothesis supporting its worries" about the safety of the hormones. In particular, he confirms Canada's explanation of some of the flaws of the EC's risk assessment when he notes that the SCVPH should have:

> integrated in its risk assessment the exposure of consumers to these hormones resulting from the consumption of hormone residues from animals which have not been treated by hormonal growth promoters and the [*sic*] from the daily production of these hormones by humans.

196. Dr. Boobis echoes this evaluation of the EC's risk assessment and its scientific evidence when he advises that "none of the information provided by the EC demonstrates the potential for adverse effects for humans" from meat from cattle treated with hormones. More specifically, he adds that:

> [t]he studies on genotoxicity provide no convincing evidence of potential for harm in consumers. The weight of evidence is that the hormones are not genotoxic in vivo even at doses well above those that would be present in meat from treated cattle. As such, there would be no risk of such effects in human from such exposures. The carcinogenic effects observed are entirely consistent with a hormonal mode of action that exhibits a threshold that would be well above the intake arising from consumption of meat from treated cattle. Other effects of the hormones that have been observed either in experimental animals or in exposed subjects occur at doses much higher than those to which consumers would be exposed via meat from treated

cattle. As such, there would be no risk of such effects in humans from such exposures.

197. For his part, Dr. Guttenplan seems to suggest, but does not explicitly state, that the EC has identified the potential for adverse effects. However, his main concern is based on the SCVPH's conclusion that pre-pubertal children have lower endogenous levels of hormones, itself based on data obtained principally by the Klein assay. As discussed in Canada's comments on Question 40, there are serious doubts about the validity of this assay. Dr. Guttenplan's endorsement of the EC's conclusions about adverse effects suffers from the same shortcomings as those conclusions themselves: they both rely on scientific methodologies that have not been validated.

198. All three experts provide useful advice on the evidence that would be required to demonstrate adverse effects, such as toxicological data (Dr. Boisseau), residue data that show that consuming treated meat leads to any change in circulating levels (Drs. Boisseau, Boobis and Guttenplan), and specific epidemiological studies (Dr. Boobis). It is important to note that none of them suggests that the EC has demonstrated such evidence currently exists.

Q53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol 17β or other oestrogenic compounds in commercial preparations? Would the systematic use of these and the synthetic hormones in combination have any implications on how the scientific experiments and the risk assessments are to be carried out? If so, have the scientific materials referred to by the European Communities or relevant JECFA reports taken into account the possible synergistic effects of such combinations on human health? [see sections 4.2-4.3 of the Opinion of the SCVPH of 2002 in US Exhibit 1]

199. Both Drs. Boisseau and Guttenplan, the only two experts that addressed this question, advise that the exposure to these hormones, both alone and in combination, is so low that there is very little risk of any increase in the risk if assessed in combination. They both acknowledge that it is oestradiol 17β that is the most potent, with the addition of the others not significantly changing this potency such that the risk would increase. Therefore, once oestradiol 17β has been demonstrated not to have adverse effects when used as a growth promoter, there is little risk that adverse effects would occur if used in combination with the other hormones.

Q54. What is the acceptable level of risk reflected in the Codex standards for the five hormones at issue? How does this compare to the European Communities' stated objective of "no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion". [see para. 149 of EC Rebuttal Submission (US case)]

200. Drs. Boisseau, Boobis and Guttenplan all advise that the acceptable level of risk reflected in Codex standards is that there is no risk of adverse effects if exposure to hormones is kept below the established ADI. In that sense, as Dr. Boobis points out, the acceptable level of risk reflected in the international standards is identical to that purportedly sought by the EC through its ban.

201. While Drs. Boisseau and Guttenplan both appear to suggest that the acceptable level of risk chosen by the EC is different than that embodied in the Codex standards, a close examination of their answers reveals that the difference to which they refer is that between theoretical risk and real risk, and not between acceptable levels of protection. That is, whereas the Codex standards indicate that there is no real risk if exposure is kept below the established ADI, the EC attempts to prevent even theoretical risk. Dr. Guttenplan confirms that the EC has not addressed the actual level of risk presented by consumption of meat from treated animals, only that there is a potential risk. Dr. Boisseau also advises that the EC will not accept "any risk, even theoritical [*sic*]".

202. Dr. Boobis expresses the issue in slightly different terms that lead to the same result. He advises that there is no difference between the two levels of risk (which are otherwise identical in that they accept zero risk to consumers of meat from treated animals) but there is a difference in how the evidence has been interpreted. On the one hand, in light of its conclusions that there is a threshold below which no adverse effects will result, Codex has adopted a standard that will not result in risk. On the other hand, in light of its conclusions that there is not a threshold below which adverse effects will not result, the EC has adopted a measure that it considers will not result in risk. To the extent that the experts in their answers to other question advise that the EC has not demonstrated that there is not a threshold, the EC has also not demonstrated that the international standards is insufficient to achieve its acceptable level of risk, which is identical to that embodied in the international standards.

203. The distinction made by the experts between theoretical risk and real risk is an important one in the context of this dispute also because it confirms that the sole reason for the EC to adopt a ban, rather than establish maximum acceptable exposure levels, was to avoid a theoretical risk, something that the Appellate Body has confirmed is not permissible under the *SPS Agreement*.

Q55. Do the Opinions of the European Communities or other scientific materials referred to by the European Communities evaluate the extent to which residues of growth promoting hormones in meat contribute to what the European Communities calls "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings"? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 151 of EC Replies to Panel Questions, paras. 43-44 of US Rebuttal Submission, paras. 83-85 of Canada's Rebuttal Submission]

204. Drs. Boisseau, Boobis and Guttenplan confirm that the EC did not evaluate additive risks. Dr. Boisseau's answer suggests that he believes the EC's "position of principle" (that it would not accept even any theoretical risk) prevented it from even trying to assess the "additive risks". Dr. Boisseau only partly answers the question, in that he only assesses the EC's decision not to compare hormone levels in treated meat versus untreated meat; he does not comment on the EC's failure to compare the effects of hormones from treated meat to the effects from all other sources of hormones, including endogenous production.

205. In the first sentence of his response, Dr. Guttenplan agrees that the EC did not evaluate "additive risks". It is not entirely clear, however, how his reference to the EC's comparison of exposure to hormones from treated meat and the background levels in prepubescent children is relevant to the evaluation of "additive risks". In fact, if anything the EC's selective evaluation of purported risks to sensitive populations from hormones from treated meat simply confirms that the EC has not evaluated "additive risks", because it has not conducted a similar evaluation of the risks posed by exposure from other sources of hormones, many of which are far greater than that from treated meat.

206. For his part, Dr. Boobis distinguishes between "aggregate risk" (risk resulting from the aggregate exposure from all sources of a single substance) and "cumulative risk" (risk resulting from the cumulative exposure from all substances with a common mechanism of toxicity) and then confirms that the EC evaluated neither kind of risk. Dr. Boobis explains that one way to assess the "aggregate risk" from exposure to exogenous sources of substances that are also produced endogenously is to determine the tolerable upper intake level taking into account endogenous production, then determine whether exogenous sources change the circulating levels of the substances in the body. JECFA has essentially done this for the natural hormones when it assessed the exposure from meat from treated animals relative to the circulating levels and found that the former fell within the normal variation of the latter.

207. Dr. Boobis acknowledges that a critical issue in assessing additive risks is whether there is a threshold below which adverse effects will not occur, something the EC argues is not the case with these hormones. As discussed previously, the EC's claim that there is no threshold for adverse effects from these hormones is simply not supported by the evidence. Therefore, its claim, from a "position of principle", that there are "additive risks" is similarly not credible in the absence of a quantitative evaluation of those risks. Indeed, the advice from the experts confirms Canada's identification of a critical flaw in the EC's claim that hormones from treated meat present an "additive risk": additive to what? In other words, what is the baseline risk from endogenous sources of hormones, or from other exogenous sources? Does exposure to hormones from meat from treated animals alter that risk? The EC does not ask, let alone answer, any of these questions, so it is difficult to see how its answer to the issue of additive risk can be legitimate.

Q56. Has JECFA/Codex considered in its risk assessment of the five hormones such "additive risks? Are there internationally recognized guidelines for conducting assessments of "additive risks"?

208. Two of the three experts who responded to this question, both of whom are quite familiar with the work of JECFA, advised that JECFA does take into consideration "additive risk" (covering what Dr. Boobis refers to as "aggregate risk" but not "cumulative risk"). The manner in which JECFA does so is similar to the process described above in Canada's comments on the responses to Question 55. That is, because there is such a wide "margin of safety" (Dr. Boisseau) between the exposure from hormones from treated meat and the aggregate exposure from all other sources (both endogenous and exogenous) and because the increase in aggregate exposure from consuming meat from treated animals was considered to be "trivial" (Dr. Boobis), there would be no "additional risk" over that from background levels.

Q57. Canada comments that "one single molecule that the European Communities considers so dangerous from meat derived from animals treated with hormone growth promoters is suddenly not at all that dangerous when consumed from meat from animals treated for therapeutic or zootechnical purposes. The European Communities' concern about the genotoxic potential of oestradiol 17β suddenly and inexplicably disappears." To what extent are hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes, taken into account by the European Communities, if at all, in its assessment of the cumulative effects from the consumption of meat containing residues of the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 97 of Canada Rebuttal Submission; paras. 17-20 of US Opening Statement]

209. Drs. Boisseau, Boobis and Guttenplan indicated that the EC did not take into account in its risk assessment the risks that arise from the use of these hormones for therapeutic purposes. Both Drs. Boisseau and Boobis share Canada's difficulty in reconciling the EC's conclusion that there is no threshold below which there are no adverse effects from hormones from treated meat and its authorization of the use of these substances for certain purposes and not others. Dr. Boisseau considers it a "problem of principle", whereas Dr. Boobis suggests that the only way this is justified is if one assumes that there is a dose-response relationship, something the EC rejects. Dr. Guttenplan fails to support his observation that the EC's explanation for why it allows such use is "reasonable". On the whole, the experts' advice indicates that the EC is trying to have it both ways: that hormones are genotoxic for some purposes and not others.

Q58. Please comment on the EC statement in para. 94 of the EC Replies to Panel Questions that "the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be", taking into account para. 105 of Canada Rebuttal Submission.

210. Drs. Boisseau, Guttenplan and Boobis all expressed in their own ways some difficulty with this statement by the EC. Dr. Boisseau suggests (with reference to his answer to Question 55) that this constitutes simply a "position of principle", one not supported by evidence that there are additive risks from higher doses of these hormones. Dr. Guttenplan simply offers that it is "indeed a very weak statement". His further suggestion that it is nonetheless better than an estimate of risk that is "wildly inaccurate" only reinforces Canada's concern that there is simply no basis for the EC to draw such a conclusion. Dr. Boobis confirms again that this statement is not supported by the evidence in that "within quite broad limits, higher exposure would not result in an increase in risk". Considering that hormone intake from meat from treated cattle represents only 1.5% of the ADI (the level below which there is no risk), it simply cannot be "inferred from the available scientific data" that exposure to more residues from meat from treated animals will lead to greater risk.

Q59. Does the scientific evidence referred to by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see para. 132 of Canada Rebuttal Submission]

211. While the three experts that responded to this question all acknowledge that there can be adverse effects on the immune system from hormonally active substances, they all confirm that there is no scientific evidence that such effects will occur from exposure to doses of hormones that would be expected from residues in meat from treated animals. Dr. Boobis points to the "margin of safety" inherent in the dose relative to the background level; Dr. Boisseau indicates that the EC has not conducted the "quantitative risk assessment" that would be required to demonstrate risk from what are known to be dose-dependent adverse effects; and Dr. Guttenplan simply cites the absence of "definitive studies" (although he could have just as easily referred to the absence of "any studies") of low dose adverse immune system effects. All of the experts therefore confirm that for the EC to demonstrate that there are risks of adverse effects to the immune system from hormones from treated meat, it would have to demonstrate that such exposure would surpass the threshold at which such adverse effects would occur. It has not.

Q60. Does the scientific evidence referred to by the European Communities identify and evaluate whether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives (MGA) or implanted? Are you aware of any differences?

212. Drs. Boisseau, Boobis and Guttenplan all indicate that the EC did not demonstrate that the potential for adverse effects differs depending on the route of administration. Only Dr. Boobis indicates that there may be a difference in effect as a result of misuse and abuse of implants, which would not occur in feed additives. However, he only acknowledges that the level of the exposure may be greater, and not that the level of risk of adverse effect necessarily would be greater. For the level of risk of adverse effects to be different, the exposure from one source of administration or the other would need to exceed the ADI, something that is quite unlikely to happen.

Q61. In your view and in the light of information provided by the parties as well as the work undertaken at JECFA and Codex, did the scientific evidence available to the European Communities at the time it adopted its Directive (September 2003) allow it to conduct an assessment (quantitatively or qualitatively) of the potential for adverse effects on human health arising from the consumption of meat from cattle treated with (a) progesterone; (b) testosterone; (c) trenbolone; (d) zeranol; and (e) melengestrol acetate? Would your response

differ in light of the scientific evidence provided which is subsequent to the adoption of the EC Directive?

213. Both Drs. Boobis and Guttenplan indicate that sufficient scientific evidence was available to the EC to conduct a risk assessment of the five other hormones. Dr. Boisseau indicates that he is unaware of what the EC had available to it at the time, but goes on to suggest that it is never possible to eliminate all scientific uncertainty, and that the EC could have obtained any information it felt it did not have. Dr. Guttenplan specifically, and Dr. Boobis through reference to his other answers, both point to work done by JECFA as establishing that the data are complete enough to conduct risk assessments. It also seems to be the case, especially from Dr. Boobis' reference to his other answers, that since there is sufficient evidence to demonstrate the safety of oestradiol 17β , which is considered to be the more potent substance, the same type of data and principles of analysis that demonstrate the safety of this substance indicate that the other five hormones will also be safe.

Q62. Does the scientific evidence relied upon by the European Communities support the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why?

214. While Drs. Boisseau, Boobis and Guttenplan all indicate that new scientific evidence has raised new and interesting issues, they do not agree that this evidence suggests important gaps in the understanding of the safety of these substances. Dr. Boisseau does not believe that these new data are contrary to previous conclusions or that they make it impossible to conduct a risk assessment. Dr. Guttenplan suggests some new areas of potential study, but some of them are already answered (see, for example, Dr. Boobis' review of the effect of consuming meat from treated animals on blood levels of oestrogen); some of them are not necessary for the completion of a risk assessment; and at least one of them (epidemiological studies of consumption of treated versus non-treated meat) will never be able to demonstrate the linkages that Dr. Guttenplan would like to see (see discussion of confounding factors above). Dr. Boobis provides the most comprehensive assessment of the new scientific data, and addresses each and every study that the EC claims raise new scientific issues. As a result of his review, he concludes that the additional information "was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded upon previous knowledge".

III. COMMENTS ON INTERNATIONAL ORGANIZATION REPLIES

Q1. Please briefly describe the procedure for the elaboration and adoption of an international standard by Codex. What is the decision-making process for the adoption of an international standard?

215. Canada has no comments to make at this time.

Q2. Please briefly explain the differences between Codex standards, codes of practice, guidelines, principles and other recommendations.

216. Canada has no comments to make at this time.

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

217. See Canada's comments on the experts' answers to Question 3.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

218. See Canada's comments on the experts' answers to Question 4.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) as defined by Codex and explain how they differ.

219. See Canada's comments on the experts' answers to Question 5.

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

220. See Canada's comments on the experts' answers to Question 6.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? [see Canada's comments in para. 72 of its Rebuttal Submission]

221. See Canada's comments on the experts' answers to Question 7.

Q8. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "...while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents..."? [see Exhibit CDA-25]

222. See Canada's comments on the answers from the experts to Question 37.

Q9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

223. See Canada's comments on the answers from the experts to Question 8.

Q10. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please also identify and describe any steps that are taken in the risk assessment process to build a margin of safety into to the final recommendation.

224. See Canada's comments on the answers from the experts to Question 8.

Q11. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA

considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

225. See Canada's comments on the answers by the experts to Question 9.

Q12. In para. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

226. See Canada's comments on the answers from the experts to Question 10.

Q13. With respect to the data used in the evaluation of chemical substances, such as the hormones at issue, what are the data requirements for JECFA's work and how are they determined? Who provides data for such evaluations? Are any records/archives kept by JECFA? Do any confidentiality rules apply to data submitted to JECFA or should all data be publicly available? If confidentiality rules apply, in which circumstances? [see paras. 95-96 of EC Rebuttal Submission (US case), paras. 78-79 of EC Rebuttal Submission (Canada case), para. 123 of Canada Rebuttal Submission]

227. JECFA confirms in its response that "[u]npublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA", and that "confidential data will either be returned to the submitter at the submitter's expense or destroyed after the evaluations have been completed."

Q14. How are experts involved in JECFA's work selected? What are the selection criteria?

228. Canada has no comments to make at this time.

Q15. Please provide the definition of the term Good Veterinary Practice (GVP). Are there any relevant Codex standards, guidelines, or recommendations relating to GVP?

229. See Canada's comments on the responses from the experts to Question 44.

Q16. Please provide an update on the status of international standards with respect to the six hormones at issue. What are the remaining procedures before the adoption of a standard on melengestrol acetate (MGA)? What is the timeframe for their completion?

230. Canada has no comments to make at this time.

Q17. Is the table in Exhibit CDA-32 outlining the chronology of JECFA's assessment of the hormones at issue and the resulting documentation complete?

231. JECFA confirms that, with the addition of a reference to the 66th JECFA meeting held 20-28 February 2006 , at which meeting JECFA further deliberated on the MRLs previously proposed for MGA, Exhibit CDA-32 is complete.

Q18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

232. See Canada's comments on the answers by the experts to Question 33.

Q19. What would be the procedures for requesting JECFA to re-evaluate its recommendations in light of new concerns/evidence? How would an amendment be adopted? Has the European Communities approached JECFA for this purpose with respect to the hormones at issue in this case? [see Exhibit EC-63]

233. JECFA's response states that "[t]he re-evaluations of compounds follow the same procedure as an evaluation performed for the first time, with clear identification of the new data that were assessed." See also Canada's comments on the answers from the experts to Question 33.

Q20. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by CCRVDF? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

234. See Canada's comments on the answers by the experts to Question 33.

Q21. What is the mandate of the International Agency for Research on Cancer?

235. Canada has no comments to make at this time.

Q22. Who are the members of the IARC?

236. Canada has no comments to make at this time.

Q23. What are IARC Monographs? How are they prepared?

237. Canada has no comments to make at this time.

Q24. Please briefly explain the groupings that are used to categorize "potentially carcinogenic agents"? What are the implications when an "agent" is placed in one of the IARC categories?

238. The Panel may wish to request further explanation from IARC regarding the considerations that determine the classification by IARC of a substance as belonging to Group 1, 2A or 2B, as well as the consequences or implications of such a classification.

Q25. Which of the six hormones at issue in this dispute (oestradiol 17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate) have been evaluated by the IARC? Have any specific risks from the consumption of meat from cattle treated with these growth promotion hormones been assessed by the IARC?

239. IARC's response states that it has evaluated the three natural hormones but not the three synthetic hormones. IARC's evaluation and classification of the three natural hormones appears not to have taken into account the different potential sources of these hormones and the different potential levels of exposure of individuals. Thus the kind of risk assessment that was conducted by JECFA was apparently not carried out by IARC. IARC does not respond to the question about the specific risks from exposure to residues of hormones in meat from treated animals.

Q26. How does the work of the IARC feed into the work of national regulatory agencies or international bodies, in particular with respect to assessments of risks from the consumption of meat from cattle treated with the six growth promoting hormones at issue in this dispute?

240. IARC's response to Question 26 is the same as that to Question 25.

IV. CONCLUDING COMMENTS

241. The experts and international bodies have provided extensive advice on the scientific and technical matters at issue in this dispute. The experts' responses exhibited general agreement that the scientific evidence and information does not support the conclusions of the EC's evaluation of these six hormones. While this is the case for most of the issues addressed by the experts, several issues that are central to the Panel's review of the EC's evaluation warrant specific mention.

242. In particular, the experts indicate that the scientific evidence does not support the following conclusions:

- that all or some of the hormones (but in particular, oestradiol 17β) present a risk of adverse effects (such as genotoxicity) that do not exhibit an exposure dose below which they will not occur (*i.e.*, a threshold);

- that exposure to the hormones from residues in meat from treated animals will be so significant in proportion to the endogenous hormone levels present in certain sensitive populations such that adverse effects will occur;

- that the exposure from this single source of hormones is sufficiently "additive" to the exposure from all sources of hormones to increase the risk of occurrence of adverse effects;

- that the failure to follow GVP will result in exposure to the hormones at doses capable of causing adverse effects and that the hormones are administered in Canada in a manner that fails to follow this GVP; and

- that the scientific evidence is insufficient to conduct an assessment of the safety of the five hormones other than oestradiol 17β.

243. Canada looks forward to meeting with the experts and to the opportunity to discuss these and other scientific and technical issues in more detail.

ANNEX F-5

COMMENTS BY CANADA TO THE COMMENTS OF THE EUROPEAN COMMUNITIES ON THE REPLIES OF THE SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC TO QUESTIONS POSED BY THE PANEL

(12 July 2006)

TABLE OF CONTENTS

I. INTRODUCTION

1. Canada is pleased to have this opportunity to comment on the comments by the European Communities (EC) on the responses by the experts and by JECFA, Codex and IARC. Before turning to comments on the specific responses, several issues of a general nature raised by the EC warrant mention.

2. First, the EC suggests in many of its comments that it is either Canada or the experts that need to demonstrate that adverse effects will not arise from consuming residues of hormones in meat from treated animals.[1] It is important to recall that it is the EC that has adopted bans on these hormones as growth promoters on the basis that they cause adverse effects, and it is the EC that has brought this case against Canada, alleging that these bans are justified under the *SPS Agreement*. Any suggestion

[1] For example, see EC Comments on the Replies by the Panel Experts, in relation to Questions 18, 20 and 59 (EC Comments).

by the EC that the burden is on Canada to prove that adverse effects will not arise runs contrary to the applicable WTO rules on the allocation of burden of proof. Similarly, any suggestion by the EC that the experts must demonstrate that such adverse effects will not arise demonstrates a misunderstanding of the role of the experts in these proceedings.

3. Therefore, it is the EC – and not Canada or the experts – that must demonstrate that it has scientific evidence that supports its claim that adverse effects will arise from consuming residues of hormones in meat from treated animals. Consequently, the focus of the discussion should not be on the manner of adoption of the international standards and their scientific underpinnings but rather on the EC's opinions and whether they meet the requirements of the *SPS Agreement*.

4. Second, the EC makes a number of assertions in its comments that that are accompanied by citations of articles that have not been filed as exhibits. Canada has been able to locate some of the articles, but not all of them and, accordingly, limits its comments to those it has been able to locate. However, to the extent that the EC refers to this material in relation to claims about scientific evidence that it is making for the first time, and then fails to provide the supporting material, the claims remain no more than unsupported assertions that should be given no weight by the Panel.

5. Third, in its comments on certain experts' responses, the EC questions the relevance of the views of Dr. Boisseau and Dr. Boobis because, according to the EC, they did not carry out "experiments on hormones" and publish related scientific papers.[2] The *curricula vitae* of both these experts, which demonstrate extensive experience in the risk assessment of many veterinary drugs as well as other chemicals, and the quality of their replies, speak for themselves. While it is the EC's prerogative to disagree with the answers provided by any of the experts, there can be no doubt about the professional competence of Dr. Boisseau and Dr. Boobis that underlies their answers to the Panel's questions.

6. Fourth, the EC tries to impugn the comments from Codex and JECFA, but not those from IARC, by questioning the legality of the transmittal of these comments by the Codex and JECFA Secretariats respectively to the Panel, without having complied with internal procedures that were not identified by the EC. It would not be appropriate for the Panel to inquire into the question of compliance with the internal rules of other international bodies. Also, the information provided by the Codex and JECFA Secretariats are matters of public record. In any event, it would be open to the EC to take any steps it deems appropriate within Codex and JECFA to deal with this issue.

7. Canada will address the EC's comments on the responses of the international bodies in Part III of this submission.

8. And finally, given the short time-frame for the preparation of these comments, the absence of comments by Canada on certain assertions by the EC should not, of course, be construed as agreement with such assertions.

II. COMMENTS ON THE COMMENTS FROM THE EC ON THE RESPONSES FROM THE EXPERTS

A. GENERAL DEFINITIONS

9. In its comments on the experts' responses to **Question 1**, the EC quibbles with Dr. Boisseau's definition of the hormones at issue in this dispute. To the extent that the issues raised by the EC are relevant, Canada will address them below.

[2] *Ibid.*, Questions 2, 17, 21 and 42.

10. The EC's attempt to discredit Dr. Boisseau's response to **Question 2** by referring to his earlier indication of which questions he intended to answer is unjustified. Other experts, such as Dr. Cogliano and Dr. de Brabander, answered questions that they did not originally indicate they would answer; some of them in the end declined to answer questions they had earlier indicated they would answer. That is the experts' prerogative and nothing more should be read into an expert responding or not responding to particular questions.

B. RISK ASSESSMENT TECHNIQUES

11. In its comments on the experts' responses to the Panel's Questions in this section (**Questions 3-12**), the EC raises several issues that warrant comment at this stage. These are:

- the meaning of the phrase "risk assessment techniques developed by the relevant international organizations", as found in Article 5.1 of the *SPS Agreement* and its relevance to this dispute;
- the relevance of the different mandates of the European Medicines Agency's Committee for Veterinary Medicinal Products (CVMP) and the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH);
- the distinction between risk assessment and risk management;
- the meaning of "no appreciable risk";
- the distinction between qualitative and quantitative risk assessments and the relevance of this distinction to the meaning of "risk assessment" as found in the *SPS Agreement*;
- the existence of scientific uncertainty; and
- the relationship between weight of evidence and minority science.

"Risk Assessment Techniques" in Article 5.1 of the SPS Agreement

12. In its comments on the responses to **Questions 3, 4** and **6**, the EC attempts to dismiss the various international guidance documents identified by the experts and JECFA and Codex as being relevant to the conduct of veterinary drug risk assessments. In doing so, the EC distorts the meaning of the phrase "risk assessment techniques developed by the relevant international organizations" in Article 5.1 of the *SPS Agreement*.[3] The thrust of the EC submission is that unless an international guidance document is formally adopted by Codex it is not "legally binding" and therefore cannot constitute a "risk assessment technique" under Article 5.1 and is irrelevant.[4] However, the EC's line of reasoning is misguided. The question is not whether the "risk assessment techniques" are "legally binding" but whether the "risk assessment techniques" assist in determining whether the risk assessment at issue is "appropriate to the circumstances." For a risk assessment to be "appropriate to the circumstances", the WTO Member must "tak[e] into account the risk assessment techniques…". Failure to do so suggests that the assessment at issue is not "appropriate to the circumstances".

[3] Article 5.1 of the *SPS Agreement* reads in full "Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations."

[4] See EC Comments, Questions 3, 4 and 6.

13. To the extent that the EC is suggesting by the phrase "legally binding" that "risk assessment techniques" must be formally established by one of the international organizations listed in Annex A(3) as a "standard, guideline and recommendation", the EC is incorrect. Had the Members intended such an effect, then they would have used "standard, guideline and recommendation" in Article 5.1. The fact that they did not implies this is not the case. The use of the term "technique" suggests that the treaty drafters were referring to the technical aspects of risk assessment methodology. Some "techniques" may be embodied in a formally established "standard, guideline, and recommendation", while others may not. The "risk assessment technique" must be "developed by the relevant international organization." Without question, Codex is a "relevant international organization". Given that Codex relies on the work of JECFA to conduct risk assessments and develop risk assessment techniques for food additives, contaminants and veterinary drugs, it can be inferred that JECFA is a "relevant international organization" for the purposes of Article 5.1.

14. In this case, "risk assessment techniques" developed by Codex include the four steps of the risk assessment process (hazard identification, hazard characterization, exposure assessment and risk characterization). Those developed by JECFA are embodied in EHC 70[5] and the JECFA Procedures.[6] More specific to this case are techniques such as the assessment of the quality and quantity of available study data, determination of pivotal studies and the NOAELs (No Observed Adverse Effects Levels), the conduct of the dose-response assessment, the selection of appropriate safety factors and the establishment of ADIs (Acceptable Daily Intakes). Therefore, assessments of veterinary drugs that fail to take into account these techniques are not, *prima facie*, "appropriate to the circumstances" and, therefore, do not satisfy the requirements of Article 5.1 and the definition of risk assessment in Annex A(4).

Relevance of the different mandates of the CVMP and SCVPH

15. In its comments on responses to **Question 3**, the EC's attempt to discredit Dr. Boisseau's advice concerning the CVMP's ability to assess pharmacologically active substances used in veterinary medicine "without any written guideline about risk assessment" is confused and illogical. The EC appears to imply that techniques used by the CVMP in conducting risk assessments are not applicable to the work of the SCVPH on the basis that the SCVPH's mandate differs from that of the CVMP. This appears to be an indirect attempt to explain the differing conclusions reached by these committees in relation to adverse effects caused by the use of hormones in animal husbandry. However, the fact that these two committees assess different uses of the same substances has no bearing on the nature of the risk assessment techniques employed. For instance, the techniques adopted to determine whether oestradiol 17β is genotoxic apply regardless of the use to which the substance will be put. If oestradiol 17β, when used for therapeutic purposes, has a dose threshold, it is illogical to conclude that it does not have a dose threshold when used for growth-promotion purposes. The EC cannot escape from the CVMP's conclusion that oestradiol 17β is not genotoxic by referring to different committee mandates.

Risk Assessment/Risk Management

16. The EC attempts, in its comments on responses to **Question 5**, to dismiss all the explanations provided by the experts of the three components of "risk analysis" by reiterating its previous arguments concerning the differing scope of, on the one hand, risk assessment as defined by the *SPS Agreement*, and, on the other hand, risk assessment as a component of Codex's risk analysis. As

[5] International Program on Chemical Safety, *Principles for the Safety Assessment of Food Additives and Contaminants in Food, Environmental Health Criteria 70* (Geneva: WHO, 1987) (EHC 70) (Exhibit CDA-43).

[6] JECFA, *Procedures for Recommending Maximum Residue Limits – Residues of Veterinary Drugs in Food (1987 – 1999)* (Rome: FAO/WHO, 2000) (JECFA Procedures) (Exhibit CDA-44).

Canada has explained in detail in its Rebuttal Submission,[7] the EC is attempting to insulate its SPS measure, *i.e.*, its ban on all meat and meat products derived from treated animals, from Panel review by suggesting that the "wider" risk assessment contemplated by the *SPS Agreement* includes risk management considerations and that risk management is *a priori* non-reviewable because it is related to a WTO Member's autonomous right to set its appropriate level of protection.

17. As Canada explained, the EC cannot escape the obligation in Article 5.1 of the *SPS Agreement* to base its measure on a risk assessment by claiming that a component of the risk assessment includes non-reviewable risk management considerations. The Appellate Body's statement that Article 5.1 was "intended as a countervailing factor in respect of the right of Members to set their appropriate level of protection"[8] implies that risk management and the autonomous right of each WTO Member to set its level of protection cannot be used to avoid the obligation in Article 5.1.

The concept of "Appreciable Risk"

18. The EC arguments concerning "appreciable risk" are a direct challenge to one of the cornerstones of modern risk assessment techniques widely employed by risk assessment bodies at both the national and international level. The EC attempts to discredit this concept by asserting that it is "subjective", "qualitative" and "unspecific".[9] However, these arguments reflect a profound misunderstanding of this concept and its role in the risk assessment process.

19. The phrase "without appreciable risk" is found in Codex's definition of ADI: "an estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk".[10] To understand what is meant by "appreciable health risk", or "appreciable risk", one must consider the risk assessment process as a whole. On the basis of detailed scientific experimentation, observation and analysis of empirical data, a NOAEL is set for each observed adverse effect. The NOAEL represents the dose level at or below which no adverse effect is empirically observed or measured in the target organism.

20. The NOAEL is then adjusted by safety factors to derive the ADI. If no effect is observed, then, logically, there is no observable or empirically ascertainable risk. Appreciable, in the sense used in the ADI, means observable, ascertainable or identifiable. Thus, far from being "subjective" or "qualitative", as the term is used by the EC, the identification of a lifetime daily intake that is "without appreciable risk" is based on quantitative scientific experiments that lead to objective, measurable observations. Indeed, the very purpose of the risk assessment methodology used by JECFA and Codex is to identify quantitatively the point at which risks are not observed or ascertained.

21. When "appreciable risk" is properly understood, the EC's comments do not make sense. An ADI based on "no appreciable risk" implies that there is no scientifically identifiable or ascertainable risk if the daily intake is equal to or below the ADI. Of course, the ADI does not eliminate the theoretical uncertainty that always exists as "science can *never* provide *absolute* certainty that a given substance will not *ever* have adverse health effects".[11] However, this theoretical uncertainty, or hypothetical risk, is not the kind of risk that, under Article 5.1 of the *SPS Agreement*, is to be assessed.[12] Thus, assuming that good veterinary practice is followed, the difference between the level of risk inherent in an ADI and the EC's purported "zero risk" level of protection, is not ascertainable

[7] Canada Rebuttal Submission, at paras. 55-65.

[8] *EC – Measures Concerning Meat and Meat Products (Hormones)*, Report of the Appellate Body, WT/DS26/AB/R, WT/DS48/AB/R, adopted February 13, 1998, at para. 177 (*EC – Hormones*).

[9] See EC Comments, Questions 8, 16, 25 and 54.

[10] See Codex's reply to Panel IO Question 9 [emphasis added].

[11] *EC – Hormones*, at para. 186 [emphasis in original].

[12] *EC – Hormones*, at para. 186.

or identifiable risk, but theoretical or hypothetical and is not the kind of risk to be assessed under Article 5.1.

Quantitative and Qualitative Risk Assessments

22. In its comments on the responses to **Questions 11**, **16** and **36**, the EC attempts to neutralize the evidence of Dr. Boisseau and Dr. Boobis concerning the distinction between quantitative and qualitative risk assessments by claiming that the Appellate Body has confirmed that qualitative risk assessments are "acceptable" under the *SPS Agreement*. However, as Canada explained in its Rebuttal Submission, although the Appellate Body concluded that a risk assessment need not establish a "minimum magnitude of risk" in order to be consistent with Article 5.1, it did not discuss qualitative and quantitative risk assessments, writ large.[13] Thus, the EC's attempt to deduce from this conclusion the more general proposition that a qualitative risk assessment is acceptable, *a priori*, under the *SPS Agreement* distorts the conclusions of the Appellate Body. The critical question is whether the risk assessment at issue evaluates the potential for adverse effects in a manner "appropriate to the circumstances … taking into account risk assessment techniques developed by the relevant international organizations". If the nature of the substance is such that no threshold for adverse effects can be established, then a dose-response assessment is not necessary. However, when scientific evidence demonstrates, as it does in this case, that a dose threshold below which no adverse effects occur can be established for the substance in question, a risk assessment that fails to include a quantitative dose-response assessment would not be "appropriate to the circumstances."

The existence of Scientific Uncertainty

23. In its comments on the experts' responses to **Question 12**, the EC attempts to impugn the use of safety factors to address certain types of scientific uncertainty.[14] It suggests that where new scientific evidence casts doubt on previous scientific conclusions, safety factors cannot adequately compensate for the resulting uncertainty. Whether this assertion is correct as a matter of principle is debatable; in any event, it does not apply in this case. As the experts have amply demonstrated, the "new" scientific evidence referred to by the EC does not call into question the scientific conclusions concerning the potential for adverse effects from residues of hormones in meat from treated cattle, particularly conclusions relating to their carcinogenic potential. The EC is simply trying to create scientific uncertainty where there is none.

The relationship between "weight of evidence" and minority scientific opinion

24. In its comments on the experts' responses to **Question 12**, the EC highlights Dr. Boobis's use of the term of "weight of evidence" and seeks to equate the term with "mainstream scientific views". The EC further suggests that using a "weight of evidence" approach forces WTO Members to dismiss or ignore minority scientific views. These arguments reveal a misunderstanding of the term as used in the context of risk assessments. The term "weight of evidence" is a term of art used to characterize the interpretation of all scientific evidence relevant to the causal hypothesis under review, in drawing conclusions about causal relationships. Not all scientific evidence will be of equivalent importance, or weight, in providing information about presence or absence of a causal relationship. A "weight of evidence" approach involves assessing the relative strength and conclusiveness of all relevant data, including the quality of testing methods, size and power of study design, consistency of results across

[13] Canada Rebuttal Submission, at paras. 81-82. Also see *EC – Hormones*, Report of the Appellate Body, at para. 186.

[14] The EC does not appear to suggest that the use of safety factors is inappropriate to address the scientific uncertainty arising from inter-species and intra-species variability. Had it done so, it would be challenging a fundamental risk assessment technique widely employed by its own scientific committees and regulators.

studies, and biological plausibility of exposure-response relationships and statistical associations. It is not equivalent to "mainstream scientific views", but is a process that should underpin the formation of scientific opinions generally, be they mainstream or minority, in order to ensure that they are scientifically sound. Dr. Boobis appears to use "weight of evidence" to indicate that the EC conclusions were not based on an evaluation of all pertinent scientific evidence, including an assessment of the relative strength of that evidence.

C. ASSESSMENT OF OESTRADIOL 17B

25. The EC makes several comments on the experts' responses to **Questions 13** and **14** that warrant further comment. These include the EC's: 1) inaccurate and misleading descriptions of the adverse effects it purports to have identified; 2) exaggeration of the role of epidemiological studies in risk assessments of the kind appropriate to these circumstances; 3) repeated attempt to embellish scientific results to demonstrate *in vivo* genotoxicity from oestradiol 17β; and 4) unjustified reliance on several new scientific studies and its criticism of the experts for failing to take these into account.

Inaccurate and misleading descriptions of the purported adverse effects

26. In response to the advice from the experts under **Question 13** that the SCVPH opinions do not amount to a risk assessment, the EC makes several confusing assertions about the nature of the adverse effects that it purports to have identified. In particular, on several occasions it uses interchangeably the terms ‘carcinogenicity' and ‘genotoxic effect', linking them both to the interaction of these hormones with hormonal receptors.[15] The EC's description of the issues is both wrong and misleading, so for purposes of restoring clarity to the issues it is useful to restate the basic controversy related to the potential carcinogenicity of these hormones and to summarize the advice of the experts.

27. The claim made by the EC is that oestradiol 17β is carcinogenic because it both initiates tumours and promotes tumour growth, the former through a hypothesized genotoxic effect and the latter through interaction with hormonal receptors.[16] To the extent that the international scientific authorities and the experts consulted by the Panel agree with the general proposition that oestradiol 17β is carcinogenic, they unanimously attribute this effect exclusively to its interaction with hormone receptors.[17] At the same time, the experts have confirmed again that there is no scientific evidence demonstrating that oestradiol 17β initiates tumours through a genotoxic effect.[18]

28. The distinction between these two different mechanisms of carcinogenicity is an important one because the findings of receptor-mediated carcinogenicity by JECFA, IARC and other scientific authorities have been exclusively attributed to circumstances involving high dose exposure to hormones, something that is clearly not a factor in exposure to dietary sources of hormones, including that from residues in meat from treated cattle. The EC's careless interchanging of the mechanisms of action and the role of dose is simply an attempt to confuse the scientific evidence related to carcinogenicity.

[15] See EC Comments, at p. 12 (Question 13).

[16] The EC's claim in its comments that the "genotoxic effect of oestradiol 17β is associated with its hormonal activity" [emphasis added] is simply nonsensical. *Ibid.*

[17] Canada's Rebuttal Submission, at paras 90-95.

[18] The EC's statement that the "carcinogenicity of estrogens is primarily due to oxidative stress/DNA adduct formation caused by the catechols [*sic*] metabolites of estrogens" is unsupported by any of the evidence submitted by the EC and is not supported by the experts. *Ibid.*

Role of epidemiological studies

29. The EC on several occasions in its comments relies on the results of epidemiological studies,[19] in particular those conducted or sponsored by IARC, as well as those on which the 2002 US Report on Carcinogens was based, as the central support for its claims that it has identified and evaluated adverse effects from the consumption of meat from treated animals. In doing so, the EC vastly overestimates the role of epidemiological studies in risk assessments of the kind required in these circumstances, that is, of exposure to substances in such small doses.

30. None of the studies cited by the EC purports to identify a relationship between cancer and residues of hormones from meat derived from treated animals. It is true that in 1987 IARC classified steroidal oestrogens as a Group I carcinogen on the basis of observed relationships between cancer and treatments using high doses of oestrogens.[20] However, the Appellate Body has already specifically rejected the claim that this classification demonstrates anything about the substances at issue here. In upholding the findings of the panel, it found that the IARC Monographs:

> constitute general studies which do indeed show the existence of a general risk of cancer [from oestrogen]; but they do not focus on and do not address the particular kind of risk here at stake - the carcinogenic or genotoxic potential of the residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes -- as is required by paragraph 4 of Annex A of the *SPS Agreement*.[21]

31. Since that time, IARC further classified postmenopausal oestrogen therapy[22] and combined oral contraceptives[23] as Group I carcinogens, again on the basis of observed relationships between cancer and these treatments. However, what all of these classifications have in common is that they involve prolonged, high dose exposure to various forms of oestrogen. Therefore, the reasoning used by the Appellate Body in the above excerpt applies equally to the EC's invocation of more recent IARC findings, as well as to any use of other findings that are based on the results of epidemiological studies.

32. As the experts have confirmed,[24] it is simply not possible to draw specific conclusions about adverse effects from residues of hormones in meat from treated animals on the basis of epidemiological studies. For that reason, these kinds of studies have limited usefulness in a risk assessment of the nature required to justify the EC's measure. They may help in identifying possible adverse effects, but they reveal nothing about the potential for occurrence of such adverse effects from a single dietary source of hormones.

33. The EC's claim that epidemiological studies, such as those on which IARC's classification of oestrogen as a carcinogen are based, support its claim is all the more surprising in light of its subsequent comment on Dr. Guttenplan's response to **Question 13**. The EC comments that it:

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[19] See EC Comments, at pp. 12 (Question 13), 20 (Questions 20), 23 (Question 23) and 24 (Question 24).

[20] *EC – Hormones*, Report of the Appellate Body, at paras. 199-200. Also, the note attached to IARC's classification indicates that this "evaluation applies to the group of compounds as a whole and not necessarily to all individual compounds within the group" (online: http://monographs.iarc.fr/ENG/Classification/crthgr01.php).

[21] *Ibid*., at para. 200.

[22] IARC, Vol. 91, Monograph No. 2, Section 5, *Combined Estrogen-Progestogen Menopausal Therapy* (Lyon, France: 2005) (Exhibit CDA-48).

[23] IARC, Vol. 91, Monograph No. 1, Section 5, *Combined Estrogen-Progestogen Contraceptives* (Lyon, France: 2005) (Exhibit CDA-49).

[24] See experts' responses to Question 26.

> agrees with the statement by Dr. Guttenplan that there are basically no direct epidemiological studies comparing matched populations consuming meat from untreated and hormone-treated cattle. However, apart from the ethical concerns, it is difficult to conduct such direct experiments in the presence of so many other confounding factors because of feasibility limitations for observational studies.

34. In this statement, the EC acknowledges the absence of epidemiological studies that demonstrate that there are risks from consuming residues of hormones from meat from treated animals. More importantly, the EC acknowledges the significant limitations of such studies to support such a conclusion.

Embellishment of scientific evidence related to in vivo genotoxicity

35. In its comments on the experts' responses to **Questions 7, 13** and **18**, the EC refers to several scientific studies in support of its claim that oestradiol 17β can cause genotoxicity *in vivo*. It is important to recall that the experts are very clear that evidence of *in vivo* genotoxicity, as well as evidence that the mode of action of genotoxicity is of a type that does not exhibit a threshold, are required to confirm findings of *in vitro* genotoxicity before it can be concluded that such genotoxicity is relevant to the development of cancer.[25] The studies cited by the EC do not satisfy these requirements.

36. In the first study referred to by the EC, by Bhat *et al.*, the authors conclude that their data "provide evidence that oxidant stress plays a crucial role in estrogen-induced carcinogenesis". However, as Dr. Boobis has indicated in his responses, oxidative stress as a genotoxic mode of action is of a type that is universally considered to demonstrate a threshold response, due to the "efficiency of endogenous antioxidant systems".[26] Therefore, this study does not demonstrate anything that was not already known, but simply confirms that genotoxicity can result from overwhelming the antioxidant systems with high doses of oestradiol 17β.

37. In its comments on the responses to **Questions 16, 18** and **62**, the EC introduces, also for the first time, a review by Yager and Davidson that the EC claims confirms that the "evidence is now sufficient to support a role for the estrogen metabolites which include the genotoxic, mutagenic estrogen quinones in estrogen carcinogenicity." The first point is that this article is only a review of other studies so provides no new evidence on its own. Second, like the studies conducted by Bhat *et al.*, this review postulates an oxidative stress damage pathway for genotoxicity, which, as noted above, is considered to have a threshold.

New scientific material cited by the EC and the role of the experts' advice

38. In its comments on the experts' replies to **Questions 13** and **14**, the EC cites a number of additional studies to support claims made in its comments and in earlier submissions. Some of these studies are introduced by the EC for the first time in its comments, very few of them were considered by the SCVPH in its opinions, and most of them do not support the specific claims made by the EC about adverse effects arising from residues of hormones in meat from treated animals.

39. The EC introduces several new studies in an apparent misunderstanding of what the experts had been asked to do. In its comments on the responses to **Question 13** concerning whether the EC

[25] See experts' responses to Questions 16, 18 and 19.

[26] Dr. Boobis's response to Question 16. See also EFSA, *Opinion of the Scientific Committee on a Request from EFSA Related to a Harmonised Approach for Risk Assessment of Substances which are both Genotoxic and Carcinogenic* (Request No. EFSA-Q-2004-020, adopted October 18, 2005) (*The EFSA Journal, 282, 1-31, 2005*), at p. 18 (Exhibit CDA-46).

opinions evaluate the potential occurrence of adverse effects (a question that specifically asks the experts for advice on the 1999, 2000 and 2002 SCVPH opinions), the EC raises two entirely new claims about adverse effects that were not even cited in those original opinions.

40. The first new claim is that "there seems now to be agreement" that oestradiol 17β increases the risk of "endometrial adenocarcinomas", citing a single study completed by Takahashi *et al.* in 1996, well before the completion of the EC's opinions. However, like much of the other scientific evidence relied upon by the EC, the Takahashi study examined adverse effects that result from exposure to oestradiol at doses above a certain threshold. The study presents no evidence that the levels of hormones that would be expected from meat from treated animals cause these effects.

41. The second new claim is that oestrogen plays a role in the hypothesized relationship between stem cells and breast cancer, citing a recent study by Smalley and Ashworth.[27] However, a review of this study reveals that it did not even investigate the role of "low-dose estrogens" in tissue stem cell proliferation, but simply hypothesized a relationship between stem cells and breast cancer. Quite apart from the fact that the study failed to identify adult mammary stem cells, which it hypothesized led to breast cancer, there are many other sources of oestrogen that would affect proliferation of these stem cells far more than would dietary sources of hormones. In other words, the relevance of this study to a safety assessment of these hormones for these uses is questionable. The authors themselves indicate the hypothetical nature of their findings when they conclude that "these issues are going to keep the field of mammary stem cell biology occupied for many years to come".[28]

42. The EC then goes on to present two additional studies, which were also not considered by the SCVPH, that it claims demonstrate a relationship between pre-pubertal growth and risk of breast cancer. The first study, by Lampit *et al.*, simply demonstrates that oestrogen replacement therapy for prepubertal children, already undergoing therapy to delay precocious puberty, resulted in changes to growth patterns. The EC attempts to combine these results with a second study, by Ahlgren *et el.*, that postulated a relationship, on the basis of epidemiological studies, between cancer and a number of other factors, one of which was prepubertal growth rates. The link that the EC is trying to draw between these two studies is, however, simply too tenuous to support the conclusion that the EC suggests.

43. Similarly, in its comments on the experts' responses to **Question 14** on whether the EC's opinions on oestradiol 17β follow the four steps in the risk assessment set out in the Codex guidelines, the EC argues that Dr. Guttenplan failed to take into account two studies concerning the ACI rat and ERKO/Wnt mouse. That the question was not whether new scientific evidence supports the EC's claims, but whether the SCVPH opinions follow the four steps of a risk assessment seems to have been lost on the EC. The new studies referred to by the EC do nothing to undermine the "mixed rating" that Dr. Guttenplan gave the EC's opinions.

44. The EC concludes its presentation of its new claims of adverse effects by lamenting that the new material was "not at all considered by the experts". However, the new material says nothing about meat from treated animals and, more importantly, the claims of adverse effects were not considered by the SCVPH in its opinions. Since the experts' role is not to review additional material and determine whether the hormones at issue pose a risk of adverse effects, the EC does not explain how any of this material – only introduced by the EC with its comments – is relevant to the issue of whether the SCVPH opinions amount to a risk assessment that is appropriate to the circumstances. The new studies do not change what the SCVPH did or did not do in its 1999, 2000 and 2002 opinions.

[27] See Smalley, M. & Ashworth, A., *Stem Cells and Breast Cancer: A Field in Transit* (2003) Vol. 3 online: www.nature.com 832-844.

[28] *Ibid.*, at p. 843.

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

45. In its comments on the experts' responses to **Question 15**, the EC only explains half the story about the Appellate Body's interpretation of the term "potential". By suggesting that the Appellate Body found that a risk assessment need only identify whether adverse effects are "possible", the EC has attempted to reduce the requirements of a risk assessment to only its first step, the hazard identification.[29] To accept the simplistic definition of "potential" as "possible" eliminates the most important element of a risk assessment, that is, the evaluation of the potential for occurrence. In the entire context of the Appellate Body's ruling, such a narrow reading is not justified. The Panel may wish to ensure that the experts are aware of the full context of the requirements of a risk assessment under the *SPS Agreement*, as set out by the Appellate Body.

46. In its comments on the experts' responses to **Question 16**, the EC again misrepresents the Appellate Body's findings related to quantitative versus qualitative risk assessments. Contrary to the EC's claim, nowhere did the Appellate Body make a finding as far reaching as a "*qualitative* assessment of risk is acceptable for the purposes of the *SPS Agreement*". As explained above,[30] what the Appellate Body said was that there is no requirement for a "risk assessment to establish a minimum magnitude of risk".[31] If the EC had identified that there was no threshold dose of hormones below which adverse effects would not occur, then it would be appropriate not to assess quantitatively the exposure. However, since the experts confirm that the EC has not demonstrated there are adverse effects that do not exhibit a threshold, the EC is required to evaluate exposure data. This requirement does not emerge from some general requirement to conduct a quantitative risk assessment, but rather from the need to evaluate the potential occurrence, even as this evaluation need not lead to the identification of a "minimum magnitude of risk".

47. In its comments on the experts' responses to **Question 17**, the EC attempts to compare the advice provided by Dr. Boisseau and Dr. Boobis to that of Dr. Lucier that was disregarded by the Appellate Body in *EC – Hormones*.[32] The comparison is not appropriate. The advice that was disregarded by the Appellate Body related to Dr. Lucier's quantification of the risk of developing breast cancer from consumption of residues of hormones in meat from treated cattle as one in every million women in Canada, the United States and Europe. The Appellate Body disregarded this calculation because it was not the result of any study that supported the risk that Dr. Lucier calculated. In others words, his specific calculation of the quantum of risk was merely unsupported speculation. This is to be contrasted with the expertise and the advice of Dr. Boisseau and Dr. Boobis on the issue of the formation of catechol oestrogens in meat. These experts are not speculating a quantum of risk, but rather are providing their expert advice on basic biological processes well within their area of expertise developed over long careers of evaluating veterinary drugs and other chemical substances.

48. With respect to the EC's comments on the experts' responses to **Question 18**, Canada has already commented above[33] on the EC's claim it has provided scientific evidence that oestradiol 17β is genotoxic *in vivo*. The EC then goes on to make the surprising and entirely unjustified claim that in any event it is Canada that must demonstrate that residues from hormones from meat from treated animals will not cause genotoxic effects. Quite apart from the fact that the EC makes no attempt to justify why Canada would bear such a burden, this assertion ignores some basic facts about this

[29] According to the international techniques for risk assessments, this is the "hazard identification" stage. According to the Appellate Body, this is the "identification of adverse effects on human health".

[30] See Canada's comments above, at para. 22.

[31] See *EC – Hormones*, Report of the Appellate Body, at para. 186.

[32] *Ibid.*, at para. 198.

[33] See Canada's Comments, Question 13.

dispute: it is the EC that claims to have found evidence that the hormones cause adverse effects; it is the EC that has adopted an SPS measure to ban these hormones as a result; and it is the EC that now claims that this measure brings it into compliance with previous findings of non-compliance. As a result, there is no question that it is now the EC that bears the burden of demonstrating that its claims are justified on the basis of scientific evidence. It has not done so, and no attempt to shift the burden to Canada alters its failure to do so.

49. In its comments on the experts' responses to **Question 19**, the EC claims that the mode of action of cancer is not relevant from a regulatory perspective. On the contrary, the mode of action is very relevant to regulators. It is also very relevant for purposes of compliance with obligations under the *SPS Agreement*, as the correct identification of the mode of action of cancer will determine whether a given SPS measure is justified by the science. If the mode of action is through hormonal activity, which clearly exhibits a threshold response, a risk assessment that ignores the existence of a threshold will not be "appropriate to the circumstances", and will not meet the requirements of the *SPS Agreement*. On the other hand, if the mode of action is through genotoxicity, regulators would be justified in eliminating exposure to the substance entirely if it were a type of genotoxic effect that did not exhibit a threshold.

50. The experts have indicated in their responses that the carcinogenic potential of these hormones is related to their hormonal activity, and also that there is no evidence of genotoxic effect *in vivo*. As a result, SPS measures (*i.e.*, the EC's bans) that are based on an assessment that as a matter of principle assumes no threshold (*i.e.*, the SCVPH opinions) can not be considered to be based on an appropriate risk assessment.

51. Furthermore, the EC's claims that there is also evidence of a relationship between exposure to oestradiol 17β during early development and the risk of breast cancer warrant further comment. The study cited by the EC in support of this claim does not specifically identify hormones from meat from treated animals as the source of exposure[34] and, more importantly, it only concludes that there "may be potential" for early hormone-induced changes to the mammary glands to be "prerequisites" for tumours. The EC therefore significantly overstates the case when it concludes that it is "beyond doubt" that there is such a link. In the absence of any evidence to support this assertion, it is simply that: an unsupported assertion. In any event, the EC does not explain the relevance of hormone exposure during early development to the experts' responses to this question, which is about the relationship between genotoxicity and the ability to establish dose thresholds.

52. In its comments on the experts' responses to **Question 20**, the EC criticizes Dr. Boobis for basing his reply on "assumptions" and "hypothesis" that oestradiol 17β is not genotoxic and that a threshold can be set. However, Dr. Boobis's advice on the genotoxic potential of oestradiol 17β is based on far more than assumptions; it constitutes his reasoned conclusions based on his experience with the issues, his review of the scientific evidence and his expertise in the area. It is the EC that bases its SPS measure on an unproven hypothesis about genotoxicity.

53. The EC also argues that it is "no longer seriously disputed" that oestradiol 17β is genotoxic, pointing again to the findings of JECFA on the matter. Canada has already addressed the significance of JECFA's findings of "genotoxic potential" in its own comments on the experts' responses to Question 20.[35] Nothing the EC has indicated in its comments changes the fact that if JECFA considered that oestradiol 17β were genotoxic, it would not have established an ADI for it.

[34] In fact, as Canada has explained in its own comments on Question 39, there are many sources of oestrogen during early development, all of which would be far greater than residues of hormones from meat from treated animals. See Canada's Comments, at para. 146.

[35] *Ibid.*, at paras. 79-82.

54. The EC also seems to believe that the issue is whether the JECFA assessments have now become outdated simply as a result of the passage of time. On the contrary, the issue is whether the EC has identified scientific evidence that the existing assessments, and the international standards based on them, cannot achieve the EC's level of protection, which is, in fact, the same as that embodied in the international standards. The focus then should be primarily on what the EC's "new" scientific evidence says about the safety of the hormones. On this point, the experts have not indicated that this new evidence changes the JECFA assessments.

55. With respect to its comments related to **Question 21**, the EC again confuses the issues by responding to a question about the genotoxic potential of the other five hormones with reference to hormone levels in prepubertal children. This response seems to suggest that the EC believes that the genotoxic potential of these hormones is dose dependent and has a threshold below which it will not occur. By lumping together its claims that depend on doses and thresholds with claims that do not depend on doses and thresholds, the EC simply demonstrates that its arguments are internally inconsistent and contradictory.

56. In its comments on the experts' responses to **Question 22**, the EC again refers to Dr. Boobis' "assumptions" about the genotoxic potential of oestradiol 17β, when in fact his advice is not based on assumptions, but on extensive evidence and opinion from the international scientific community that oestradiol 17β is not genotoxic *in vivo*.

57. With respect to its comments on the issue of DNA repair mechanisms, the EC raises concerns never before raised by it or the SCVPH about an "increase in the rate of damage". It suggests that "if the rate of repair were constant", increases in the rate of damage caused from residues of hormones would lead to increases in the rate of unrepaired damage. Quite apart from the fact that it provides no scientific evidence to support the assertion that the rate of repair is constant, and apart from the fact that the experts have all said that there is considerable redundancy in the repair mechanism, even the EC acknowledges, by presenting the issue as a hypothetical, that its assertion is completely untested.

58. In its comments on the experts'responses to **Questions 23** and **24**, the EC acknowledges what it failed to acknowledge in comments on Question 13 above, that "epidemiological studies will not be able to discriminate (or separate out) the true origin of cancer because of so many co-founding factors." It is not clear, however, why the EC believes that this acknowledgment undermines Canada's position, since Canada has never argued that epidemiological studies can prove that the hormones are safe. Rather, Canada has only ever argued that the results of epidemiological studies provide no information about causal relationships between adverse effects and consumption of hormones from meat from treated animals.

59. The EC's additional comments on the IARC studies, on which it places so much emphasis in its response to Question 13, are also notable. Even though it misrepresents what those studies actually show,[36] it still has to acknowledge that "this is just an indication that there might be a link between consumption of red meat and breast cancer". In the end, it appears that the EC and Canada agree on the limited value of epidemiological studies in the conduct of a risk assessment appropriate to the circumstances of these substances.

[36] The EC's statement that the IARC studies show that the "frequency of breast cancer in countries where hormones are allowed is higher compared with countries where the hormones have not been used" is misleading. If it is referring to IARC's classification of oestrogen as a Group I carcinogen, then the data relied upon in that conclusion did not distinguish between areas where growth-promoting hormones arre used and where they are not. In other studies, only a very selective reading of the data shows any cancer rate differences exist between such regions. To the extent these data show any differences at all, Dr. Boobis also cautions against "ecological fallacies" when interpreting such data.

60. In its comments on the experts' responses to **Question 25**, the EC again attempts to impugn the data on which JECFA relied for its assessment that exposure to the hormones at levels below the established ADI would not lead to adverse effects. It again tries to claim that simply because the data are "old", they are no longer valid, without providing any scientific evidence that contradicts the conclusions of JECFA based on those data. Dr. Boobis has not imposed a higher standard on the EC than was imposed on JECFA; he is simply indicating that the EC has failed to demonstrate scientifically, either in the three additional studies or in any other studies, that there is a potential for adverse effects.

61. The EC also again criticizes JECFA's level of protection of "no appreciable risk" as being subjective and qualitative. Not only is this criticism ironic in light of the EC's own defence of the appropriateness of "qualitative" risk assessments, but it is also wrong. As Canada has explained in its comments above on the EC's comments on risk assessment techniques,[37] "no appreciable risk" can be equally expressed as "zero observed risk". This is not 1% or 10% risk, as the EC suggests here, but is zero risk. This does not mean that there is no hypothetical risk; it simply means that no adverse effects have been observed to support a conclusion that there are risks. In other words, any risk that might be inherent in the expression "no appreciable risk" is simply a theoretical or hypothetical one.

62. In its comments on the experts' responses to **Question 26**, the EC seems to shift position once again on the value of epidemiological studies. In earlier comments, it states that epidemiological studies confirm the existence of adverse effects; in other comments, it states that epidemiological studies cannot prove one way or another that adverse effects will occur; and now it states that it relies upon the results of epidemiological studies simply to demonstrate that scientific uncertainty is growing. The only thing that seems to be uncertain is what the EC actually believes is the value of such studies in support of its claims. The EC places considerable emphasis on the statements by several experts that the results are "consistent with" an association between hormone residues in meat and cancer outcomes. However, in light of the clear advice from the experts about the inability to separate confounding factors, finding that they are "consistent with" an association says very little about demonstrable association.

(b) Residue Analysis

63. In commenting on the responses to **Question 27** concerning residues of synthetic hormones, the EC asserts that the differences in residues are "not only structural/chemical but also qualitative and quantitative." What the EC means by "qualitative" is left unclear. In terms of "quantitative" differences, the EC refers to one of the 17 studies commissioned by the European Commission conducted by Rainer Stephany and the conclusions contained therein relating to the concentration of oestradiol-17β in meat from treated cattle.[38] However, concentrations of oestradiol 17β (a natural hormone) provide no information about quantitative differences in residues of synthetic hormones, which is the focus of this question.

64. The study provides no support for the EC's suggestion that actual residue data for synthetic hormones differ from data submitted as a part of the authorization of synthetic hormones.

65. In commenting on the experts' replies to **Question 28** concerning residues of synthetic hormones, the EC attempts to discredit Dr. Boisseau's reply by asserting that "estradiol-alpha", by which the EC presumably means oestradiol-17∀ (alpha), is a main residue found in the liver of cattle treated with oestradiol 17β and that this residue gives rise to human health risks. In the next paragraph, however, the EC cites Dr. de Brabander's conclusion that residues of endogenously

[37] See Canada's comments above, at paras. 18-21.

[38] Stephany, R., *Hormones in meat: different approaches in the EU and in the USA*, (2001) 109 (Suppl. 103) APMIS S357, at p. 361 ("Stephany Study") (Exhibits EC-49, CDA-12).

produced natural hormones in cattle are in the 17α (alpha) form (inactive), while the use of natural hormones used for growth promotion "may lead to residues in the [oestradiol 17] β form (active form)". This latter conclusion suggests that, if indeed the EC is correct that oestradiol-17∀ (alpha) gives rise to human health risks (a bald proposition unsupported by any evidence), the risk comes from eating meat from untreated cattle. Dr. de Brabander does not suggest that meat from treated cattle contains a higher proportion of oestradiol-17∀ (alpha). Thus the EC's argument disproves itself.

66. In commenting on the experts' replies to **Question 29** concerning residues of synthetic hormones, the EC asserts that the SCVPH considered ADIs and MRLs (Maximum Residue Limits) recommended by JECFA and "went even further and examined tolerance levels recommended by the USA." This statement is both inaccurate and misleading. For trenbolone acetate (TBA), the SCVPH did not even refer to, let alone consider, MRLs recommended by JECFA, choosing instead to compare tolerance limits set by the US Food and Drug Administration (FDA) to JECFA's ADI.[39] Whatever the merit of this approach, it says nothing about the appropriateness of JECFA's MRLs. Moreover, the SCVPH failed completely to address JECFA's conclusions, which are in part:

> The Committee recommended MRLs for β-TBOH in muscle and α-TBOH in liver of 2 µg/kg and 10 µg/kg respectively….These MRLs are not likely to be exceeded with good practice in the use of veterinary drugs.
>
> Conservative estimates using these MRLs and the daily intake values for edible tissues given in Section 2.6 indicate that the ADI for TBA of 0.02 µg per kg of body weight should not be exceeded at any time after implantation of the drug. The maximum concentrations of residues occur at 15-30 days after implantation and are below the recommended MRLs; concentrations will be even lower at the usual withdrawal time of 60 days.[40]

67. Thus, even if withdrawal periods are not respected, the ADI would not be exceeded.

68. In relation to zeranol, the SCVPH simply refers to the MRLs set by JECFA[41] and again compares them to the US FDA tolerances. This says nothing about whether the MRLs set by JECFA would lead to intake sufficient to exceed the ADI. Nor did the SCVPH evaluate JECFA's conclusion in its residue monograph for zeranol that "[t]he total residues [of zeranol] in liver, kidney, muscle and fat do not exceed 10, 2, .2 and .3 µg/kg, respectively, at any time post-implantation".[42] Again, even if the withdrawal periods were not respected, the ADI would not be exceeded.

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[39] 1999 SCVPH Opinion, at p. 57 (Exhibit CDA-2). Surprisingly, the SCVPH used temporary ADIs set by JECFA in 1987, as opposed to the final ADI set by JECFA in 1989. The final ADIs are found in JECFA, *Evaluation of certain veterinary drug residues in food: Thirty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 788 (Geneva: WHO, 1989), at p. 62 (JECFA's 34th Report) (Exhibit CDA-19).

[40] JECFA's 34th Report, at p. 42 [emphasis added] (Exhibit CDA-19). The Residue Monograph for TBA prepared for the 34th Meeting of JECFA is found at Exhibit CDA-38.

[41] JECFA, *Evaluation of certain veterinary drug residues in food: Thirty-second Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 763 (Geneva: WHO, 1988), at p. 28 (Exhibit CDA-18).

[42] JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Thirty-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food and Nutrition Paper, No. 41/1 (Rome: FAO, 1988), at p. 46 (32nd JECFA, Residue Monograph for Zeranol) [emphasis added] (Exhibit CDA-39).

69. Lastly, in relation to MGA, the SCVPH did not consider the MRLs recommended by JECFA for MGA, let alone the detailed residue monographs for this substance.[43] It is worth noting that while the JECFA recommendations were made after the SCVPH opinions, they were made prior to the establishment of this Panel in January 2005.

70. The foregoing demonstrates that the EC, through the SCVPH, did not consider whether actual residues of the synthetic hormones in meat from treated cattle would exceed the MRLs recommended by JECFA. It also failed to consider whether compliance with the MRLs recommended by JECFA would lead to an intake of residues in excess of the Codex ADI. Thus, in this regard, the EC has not provided a scientific justification for why established international standards would not meet its chosen level of protection.

71. In commenting on the experts' replies to **Question 30** concerning residues of natural hormones, the EC again confuses and distorts the JECFA ADI. As will be discussed below,[44] although JECFA referred to background levels of circulating hormones, their daily production and metabolic clearance rates (MCR),[45] the ADI is not based on a calculation of endogenous production of natural hormones, but on the NOAEL. Therefore, even if background levels, daily production rates and MCRs of the natural hormones in prepubertal children are lower than first thought, the ADI would not be affected.[46]

72. In commenting on the experts' replies to **Question 31** concerning the variation in physiological levels of natural hormones in meat from untreated cattle, the EC again presents inaccurate information. First, the EC inaccurately states that Dr. de Brabander refers to the EC study indicating that consumption of meat from treated cattle contains 7.5 times more oestrogens than meat from untreated cattle. Presumably, the EC is referring to the Stephany Study, cited earlier in relation to Question 27. However, Dr. de Brabander never once refers to this study, nor does he provide any quantitative estimate of the amount by which natural hormones in meat from treated cattle vary from meat from untreated cattle. Second, on a more substantive level, the EC inappropriately cites the average level of oestradiol 17β as opposed to the more appropriate median value, used by the author of the study. The author writes:

> From *ad random* studies in 1998 and 1999 with meat imported from the USA to the EU or obtained from the US domestic market (25-26) it is estimated that the median dietary intake of 17β-estradiol via a 250 gram steak of "Hormone Free Cattle" is less than 2.5 nanogram and via 250 gram "beef" of "Hormone Treated Cattle" is 5 nanogram. This has to be compared with the recently found median dietary intake of 17β -estradiol of 6.5 nanogram via a 50 gram hens egg….From this comparison the

[43] JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/14 (Rome: FAO, 2002) (58th JECFA, Residue Monograph for MGA) (JECFA's 58th Report) (Exhibit CDA-35); and JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Sixty-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/16 (Rome: FAO, 2004) (62nd JECFA, Residue Monograph for MGA) (Exhibit CDA-33).

[44] See Canada's comments below, at paras. 84-87.

[45] JECFA, *Toxicological evaluation of certain veterinary drug residues in food: prepared by the Fifty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Food Additives Series No. 43 (Geneva: WHO, 2000) (Toxicological Monographs for Oestradiol-17β, Progesterone and Testosterone), at pp. 51, 82 and 90 for each hormone, respectively (Exhibit CDA-11).

[46] The EC's comments on misuse and abuse will be addressed later in these comments in the Section on GVP.

> preliminary conclusion is that hens eggs are a major source of 17β (and 17α-estradiol in the daily "normal" diet.[47]

73. Thus, residues of natural hormones in meat from treated cattle are only twice the median level found in meat from untreated cattle. Moreover, total residues of all oestradiol 17β in 250 grams of beef (approximately ½ lb) from treated cattle (5 ng) are less than that found in one egg (6.5 ng)! Not unexpectedly, the EC ignores this finding and the main recommendation of the Stephany Study that "[t]he 'hormones in meat problem' should be evaluated in relation to all facts about the actual total dietary intake of 'hormones', e.g. from meat(products), poultry, milk, dairy products, eggs, and fish(products) taking also into account the effects of various ways of food production and of 'household' cooking".[48]

74. The above results and conclusions are consistent with those of the UK Sub-Group of the Veterinary Products Committee, which reviewed data relating to the natural occurrence of steroid hormones in a variety of food sources.[49] Those data included a study by Sonja Hartmann, *et al.*, which concluded:

> Meat does not play a dominant role in the daily intake of steroid hormones…The main source of estrogens and progesterone are milk products (60-80%). Eggs and vegetable food contribute in the same order of magnitude to the hormone supply as meat does.[50]

75. The Stephany and Hartmann studies support Canada's basic point that the risks associated with hormones for growth-promotion purposes cannot be appropriately evaluated without considering exposure to other sources of dietary hormones. The data also suggest that the EC's stated high level of protection for its citizenry, particularly prepubertal children, is more rhetoric than reality. One need only consider that few prepubertal children consume anything close to 250 grams (½ lb) of beef on a daily basis, while milk products and eggs are staples of a child's diet, to see that such claims ring hollow. Given the significance of other dietary sources of hormones in comparison with the trivial contribution from the use of growth promotants, the EC's purported concerns about genotoxicity and endocrine disruption, amongst others, begin to look less and less genuine.

76. In commenting on the replies to **Question 32** concerning unvalidated detection methods, the EC criticizes Dr. Boisseau's advice as being "scientifically unsound." However, it is clear from Dr. Boisseau's reply that he is referring to the use of detection methods for determining compliance with MRLs. In that context, his statement that detection methods need only be sensitive enough to detect residues in excess of MRLs is scientifically accurate. To the extent that the "ultra-sensitive" detection methods referred to by the EC are intended to evaluate levels of naturally occurring hormones in a variety of food sources,[51] it should be recalled that data on these levels currently exist and are before this Panel.[52] Unless and until new, more sensitive detection methods are developed and

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[47] Stephany Study, at p. 361 (Exhibits EC-49, CDA-12).

[48] *Ibid*.

[49] UK, Sub-Group of the Veterinary Products Committee, *Executive summary and critical evaluation of the scientific reasoning and methods of argument adopted in the opinion of the Scientific Committee on Veterinary Measures Relating to Public Health which assessed the potential risks to human health from hormone residues in bovine meat and meat products*, October 1999, at pp. 11-12 (Exhibit CDA-6).

[50] Hartmann, S., *et al*., *Natural occurrence of steroid hormones in food*, (1998) 62:1 Food Chemistry, at p. 18 ("Hartmann study") (Exhibit CDA-50).

[51] It is unclear to what use the "ultra-sensitive" detection methods are to be put. However, one could infer from the introduction to Section 4.1 in the 2002 SCVPH Opinion that the intended use is to determine with greater precision the levels of naturally occurring endogenous hormones in the entire food basket.

[52] See UK Sub-Group Report (Exhibit CDA-6); and Hartmann study (Exhibit CDA-50).

validated that call into question the accuracy of the current data, the current data should be accepted as accurate.

77. In commenting on the experts' replies to **Question 33**, the EC implies that JECFA is keeping from the Panel and the public the residue data it relied upon during its 1999 review, thereby preventing an "open and objective" verification. One need only review the 50-odd pages of residue data summarized in the residue monograph prepared for JECFA's 52nd Meeting (summarized by Dr. Arnold from the German Federal Institute of Health, no less!) to appreciate the exaggerated and sensationalist nature of the EC's claim in this regard.[53]

78. In relation to the EC's comments on the experts' replies to **Question 35** concerning MGA and whether "subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies", it is important to recall that the MRLs recommended by JECFA in 2000 were only "temporary" pending the "receipt of information on an analytical method suitable for quantifying residues of melengestrol acetate in liver and fat tissue. This information is required for evaluation in 2002".[54] Indeed, as explained by Canada in its comments on the experts' answers (Question 29), a validated detection method was submitted and accepted by JECFA during its 58th meeting in 2002.[55] Contrary to the EC's view, these data are hardly "old" and "outdated".

(c) Dose-Response Relationship

79. In its comments on the experts' responses to **Question 36**, the EC again misrepresents the Appellate Body findings related to "quantitative" analysis, which Canada has already addressed in its comments above.[56]

80. With respect to its further claim in its comments on that question that Dr. Boobis acknowledged that no dose-response assessment may be required, it is important to note that Dr. Boobis only accepted that to be the case if two conditions were present: 1) the particular mode of action for the genotoxic effect is of a kind that does not exhibit a threshold response; and 2) it is confirmed in *in vivo* tests.[57] As Dr. Boobis advised, neither of these conditions has been met in the case of these hormones when used as growth promoters.

81. The EC then cites the absence of "internationally agreed principles" on when to conduct a dose-response assessment to justify its failure to have conducted one. However, the real issue is not whether the EC is required to do so under international risk assessment techniques but, rather, whether it is appropriate in these circumstances to fail to conduct a dose-response assessment in the course of a risk assessment. As Canada has argued elsewhere,[58] it is not possible appropriately to evaluate the potential occurrence of adverse effects from residues of hormones from treated meat without first knowing the dose at which such adverse effects will not occur.

82. With respect to the EC's comments on the experts' responses to **Question 37** concerning whether a dose response assessment is necessary, it is sufficient to note that contrary to the EC's claim Dr. Boobis and Dr. Boisseau do not agree with the EC, but rather they agree with Canada's statement.

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[53] JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12 (Rome: FAO, 2000), at 37-90, and 137-140 (Exhibit CDA-17).

[54] JECFA, *Evaluation of certain veterinary drug residues in food: Fifty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 900 (Geneva: WHO, 2001) (54th JECFA, Technical Report for MGA), at pp. 79-80 (Exhibit CDA-36).

[55] See Canada's Comments, at para. 111. Also see JECFA's 58th Report, Residue Monograph for MGA, at pp. 56-59 (Exhibit CDA-35).

[56] See Canada's comments above, at para. 22.

[57] See Canada's Comments, Question 36.

[58] See Canada Rebuttal Submission, at paras. 80-82.

To the extent that they describe any circumstances in which the statement would not be true, such as when genotoxicity is confirmed *in vivo*, those circumstances do not apply here. In fact, they clearly indicate that a dose-response assessment is critical to establishing an ADI and MRL.

(d) Sensitive Populations

83. In commenting on the experts' responses to several questions under this section, the EC makes a number of claims that reflect a misunderstanding of the relationship between the establishment of ADIs and the identification of background levels[59] and that rely too much on a single unvalidated measurement methodology (*i.e.*, the Klein recombinant cell bioassay (RCBA)[60]).

84. The EC claims in its comments on the experts' responses to **Question 38** that JECFA cannot set ADIs and MRLs without accurate data on background levels. However, nowhere – at least, nowhere that Canada can find and the EC has not provided a source – is it indicated that JECFA considers data on background levels to be "essential for determining the ADI". On the contrary, the establishment of an ADI, and hence an MRL, does not depend at all on the identification of background levels. Rather, it depends on actual observations of adverse effects at given dose levels, to which appropriate safety factors are applied to protect against variation in sensitivity between different human populations.

85. The general intention behind linking background levels with the establishment of ADIs for these hormones – which the EC does in almost all its comments in this section – is to create confusion between two distinct approaches to measuring exposure. On the one hand, there is the JECFA approach of identifying a NOAEL, applying safety factors and establishing an ADI, none of which depends on the identification of background levels. On the other hand, there is the EC's attempt to compare the proportion of intake exposure (which, incidentally, it never actually estimates) to background levels, and assert that if background levels are lower than once thought, the risk must therefore be higher simply because the ratio of intake (exogenous) dose to background (endogenous) levels would be higher.

86. At no point, however, does the EC explain this relationship. Even if the EC demonstrates background levels are lower (which it has not), since JECFA's ADI approach is based on actual observed adverse effects regardless of the background level, a change in background levels is not relevant to whether adverse effects have been observed and therefore is not relevant to the ADI.

87. To place this issue in a slightly different context, if no evidence exists that consuming an egg (which has 6ng of oestradiol 17β, an amount equivalent to that in 250 grams of beef from treated cattle) has adverse effects on the endocrine systems of prepubertal children, then studies using genetically modified yeast that suggest that the background levels of endogenous hormones in prepubertal children are lower than first thought, do not demonstrate that consuming an egg now has greater risk.

88. The experts in their responses to **Question 41** have of course confirmed that populations with lower background levels are at greatest risk of adverse effects from exposure to hormones, and they have also confirmed that this is so because the proportion of exogenous hormone levels to endogenous exposure would be greater. However, this statement of basic physiology does not in itself confirm that even if it turns out that background levels are lower than once thought, the appreciation of the risk

[59] Canada understands that for the general purposes of the review of the scientific and technical material, the term "background levels" can be used interchangeably with "circulating levels" "endogenous levels" and "physiological levels".

[60] Klein K.O., *et al*., *Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay* (1994) 94 J Clin Invest 2475–2480 (Klein RCBA).

would be greater. New test results that suggest background levels are lower than once thought simply change the understanding of the levels themselves, and not the risks of adverse effects.

89. In other words, for the purposes of establishing the ADI, the ratio that matters is not that between hormone intake and background hormone levels, but rather that between the background hormone levels of the populations used to identify the NOAEL and other subpopulations. And as the experts indicate in their answers to **Question 42**, JECFA already takes into account the expected lower background levels in sensitive populations.

90. In its comments on the experts' responses to **Questions 38, 39** and **40**, the EC makes several confusing and unfounded assertions about the validity and importance of background level data generated by the Klein RCBA. First, in its comments on **Question 38**, it discounts the importance of validation of scientific methodologies in support of scientific conclusions, claiming that the ultrasensitive Klein RCBA need not be validated at all for the results to have any importance. There is no basis for such a claim. It requires more than one unvalidated attempt to generate competing data to cast doubt on the data generated by radioimmune assays (RIA). The claim that JECFA uses data from assays that have not been validated is also unfounded. JECFA goes to great lengths to validate the quality and precision of the data on which its recommendations are based. The EC did nothing to validate the data generated by the Klein RCBA.

91. In its own comments on the experts' responses to **Question 39,** the EC seems to indicate that it does not even believe the Klein RCBA is valid, when it contradicts the comments it made on **Questions 38** and **40**. In its comments on these latter questions, the EC claims that the Paris assay results overestimate the levels compared to the Klein RCBA results. But in its comments on the question coming between these two, it supports Dr. Sippell's attempt to validate the Klein RCBA results with reference to a "number of sources confirming the values" generated by Klein. It seems to have been lost on the EC that the only "confirming" source offered by Dr. Sippell was that of the Paris assay. So, whereas the EC does not consider the Paris assay results to be credible enough to be used to demonstrate that Klein is <u>inaccurate</u> (as suggested by Dr. Boobis), the EC does believe that these results are credible enough for purposes of confirming that Klein is <u>accurate</u> (as suggested by Dr. Sippell).

92. In the end, the EC itself dispels any doubt about whether it is convinced of the validity of new methodologies for measuring background levels, or the legitimacy of the data these have produced. It sums up its concerns in its comments on both **Questions 38** and **40** when it notes that the "real values for serum 17β-oestradiol in prepubertal children still remain to be properly documented". In light of the uncertainty about the validity of the new measurements and the continued legitimacy of JECFA's ADI approach – which does not depend on these measurements – the EC has not demonstrated that JECFA's recommendations need to be modified.

(e) Bioavailability

93. In its comments on the experts' responses to the only question of this section (**Question 43)**, the EC makes the same mistake as it makes under the section on sensitive populations when it suggests that new information on bioavailability calls into question the validity of the JECFA-established ADIs. As Canada has already explained in its own comments on the experts' responses to the questions,[61] the actual amount of hormones that is bioavailable does not affect the validity of the ADI. Rather, the ADI is based on observed adverse effects from a given oral dose, which means that the ADI represents, in the words of Dr. Boobis, a "bioavailability adjusted" dose. The EC makes no comment on this concept. Instead, just as it does with the questionable re-evaluation of background levels, it also exaggerates the importance of what it considers "credible evidence" that the

[61] See Canada's Comments, at paras. 162-163.

bioavailability of hormones might be higher than once thought. Neither issue, in the end, demonstrates that the international standards would not meet the EC's chosen level of protection.

(f) Good Veterinary Practice (GVP)

94. In the *EC – Hormones* dispute, the Appellate Body found that the EC did not submit a risk assessment "demonstrating and evaluating the existence and level of risk arising…from abusive use of hormones and the difficulties of control of the administration of hormones for growth promotion purposes, within the United States and Canada as exporting countries".[62] Thus, one of the central issues in this dispute is whether, this time around, the EC has actually evaluated the potential adverse effects on human health related to the failure to comply with good practice in the use of veterinary drugs (GVP). As explained by Canada elsewhere, the EC has not done so.[63]

95. In its comments on experts' responses to questions in this section (**Questions 44-51**), the EC challenges the unequivocal conclusion of the experts that the SCVPH made "no attempt to evaluate the risks from the resultant exposures [from] misuse or abuse".[64] The EC claims that it indeed conducted a proper assessment of these risks, citing several exhibits to support its claim, the most important of which is the European Commission's *Draft Report on the Assessment of Risks of hormonal growth promoters in cattle with respect to risks arising from abusive use and difficulties of control*.[65] However, a close review of these exhibits reveals that the EC claim is profoundly flawed.

96. It is important to clarify up front a few issues concerning GVP generally raised by the EC. First, with respect to **Question 46**, the EC's attempt to discredit JECFA's assessments of these hormones on the basis that JECFA did not assess potential misuse/ abuse is unsound. As explained by Dr. Boisseau, in recommending MRLs, JECFA assumes that GVP will be followed; for practical purposes JECFA does not examine potential compliance or control issues. While the failure to follow GVP may lead to residues that exceed the recommended MRL, and to a corresponding intake of residues in excess of the established ADI, such a failure does not undermine the validity of the MRL.[66]

97. Second, in relation to **Question 48**, the EC's attempt to discredit Dr. Boobis's opinion by suggesting that he does not appreciate the distinction between "probability" and "possibility" as laid down by the Appellate Body is equally flawed.[67] The Appellate Body concluded that it is insufficient merely to identify the possibility of misuse/abuse, which is in effect all the EC did during the first *EC – Hormones* panel.[68] In correctly finding that the EC's assessment of this issue did not meet the requirements of a risk assessment consistent with Articles 5.1 and 5.2 of the *SPS Agreement*, the Appellate Body implies that a if WTO Member alleges risks to human health from failure to comply with GVP, that Member must evaluate the existence and level of risk arising from the abusive use of such a substance, not simply identify the possibility that such abusive use may occur.

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[62] *EC – Hormones*, Report of the Appellate Body, at para. 207.
[63] Canada Rebuttal Submission, at paras. 107-111.
[64] Response by Dr. Boobis to Question 48, at p. 42.
[65] European Commission, *Assessment of Risks of hormonal growth promoters in cattle with respect to risks arising from abusive use and difficulties of control*, Draft Report by special working group of external private experts and European Commission officials, Brussels, 29 April 1999 (Commission Draft Report on Assessment of Risks of Abusive Use) (Exhibit EC-73). This document was exhibited for the first time in the EC Rebuttal Submission, despite the Panel's specific request to the EC to identify the documents that encompass the risk assessment for its permanent ban. See Questions from the Panel after the First Substantive Meeting, 3 October 2005, Question 16.
[66] See Canada's Comments, Question 46.
[67] See EC Comments, Question 48, at p. 40.
[68] *EC – Hormones*, Report of the Appellate Body, at paras. 206-208.

98. Third, compliance with GVP is not an end in itself, but only a means for estimating whether actual residues in meat from treated cattle exceed recommended MLRs and/or lead to intake in excess of established ADIs. The EC devotes considerable effort to the question of whether Canada and the United States can demonstrate to the satisfaction of the EC that compliance with GVP has been assured in their respective territories, while practically ignoring the more fundamental question of whether actual residues in Canadian meat from treated cattle exceed recommended MLRs and/or lead to intakes in excess of established ADIs.

99. On a more substantive level, the EC's purported assessment of the misuse/abuse of hormones in Canada and the United States is based on a number of assumptions about both the occurrence of misuse/abuse and the risks to human health in the unlikely event that such misuse/abuse occurs. In terms of the former, the EC assumes that because there are economic incentives to using hormones for growth-promotion purposes (increased weight gain, greater feed efficiency, *etc.*), farmers will invariably misuse/abuse them in the absence of control measures as stringent as those applied in the EC. These assumptions may be based in part on the unfortunate fact that Europe has faced a "continuous series of residue scandals with illegal 'anabolic hormones' in cattle".[69] However, without concrete evidence, extrapolating illegal conduct in one's own jurisdiction to illegal conduct in another is unjustified.

100. The notion that economic incentives will invariably lead to misuse/abuse does not reflect realistic conditions of use. It presupposes that farmers are irresponsible, concerned only about profit, and insensitive to issues of animal welfare and human health. Moreover, it assumes that weight gain is proportional to the amount of hormone administered (*i.e.*, increasing the number of implants increases weight gain and the corresponding economic benefit). This assumption is not valid. It also ignores the possibility that misuse/abuse can lead to performance below optimum levels, negative effects on future reproductive performance and side effects such as vaginal and rectal prolapses. All of this demonstrates that the simplistic notion that "economic incentives" lead to misuse/abuse does not reflect realistic conditions of use.

101. Similarly, the absence of control measures as stringent as those found in Europe does not imply that misuse/abuse is more likely. Control measures are typically proportional to the magnitude of the problem. There is simply no evidence that misuse/abuse of hormones in Canada is a problem sufficient to warrant the control measures that the EC appears to deem necessary.

102. With those comments in mind, Canada will now turn to a detailed review of the assessment report contained in Exhibit EC-73. The EC asserts that higher risk flows from misuse/abuse of hormones in several ways: (a) misplaced implants, (b) off-label uses, (c) simultaneous multiple implants, and (d) black-market drugs.

103. In terms of misplaced implants, the EC postulates that tissue from the site of application containing excessive concentrations of hormones may find its way into the human food chain. The EC then presents in Table 4 of Exhibit EC-73 hypothetical exposure scenarios for various elevated concentrations of hormones and concludes that there is a risk to human health from misplaced implants.[70] This risk can occur either because the ear into which the implant has been subcutaneously inserted may not be discarded or because implants may be incorrectly inserted in edible tissues, such as the neck muscle, shoulder or hind leg. In support of this concern, the EC cites one example from Canada that found residues in muscle tissue that could only be explained by improper placement of an implant or the application of unapproved intramuscular injections of liquid hormone preparations.[71] This anomalous result hardly constitutes compelling evidence of the frequency of misplaced implants.

[69] Stephany Study, at p. 358 (Exhibits EC-49, CDA-12).
[70] Commission Draft Report on Assessment of Risks of Abusive Use, at p. 15 (Exhibit EC-73).
[71] *Ibid.*, at para. 16.

Other than this one example, there is no evidence that in Canada ears with implants are processed into food or that implants are inserted into other edible parts of the cow. The EC has merely identified a possibility, unsupported by any analysis of frequency of occurrence or assessment of the impact on human health in the unlikely event that such a possibility materializes.

104. Canada notes that the risk of excessive concentrations of hormones entering the food chain is far greater when liquid hormone preparations are injected into the muscle of the animal (intramuscular injection). However, this is far more likely a problem in countries that ban outright the use of growth promotants than in North America, where subcutaneous implants in the pinna of the ear of cattle (middle third of the back-side of the ear) are permitted. In order to avoid detection, it is reasonable to assume that European farmers using illegal anabolic steroids would likely use intramuscular injections rather than pinna implants, as the latter can remain *in situ* for up to 120 days and are easier to detect.[72] Thus, the more realistic exposure scenario for the calculations presented in Table 4 of Exhibit EC-73 is excessive exposure from residues in edible tissues (muscle and fat) resulting from intramuscular injections, a practice far more likely in Europe than in Canada.

105. In terms of off-label uses, the EC cites the presence of TBA and zeranol in veal calves (calves less than 45 days of age). This implies that some growth promotants may have been used earlier than recommended, but says nothing about the potential misuse of growth-promoting hormones later in the life of cattle.

106. In terms of simultaneous multiple implants, the EC simply fails to present any evidence relating to the frequency of inappropriate multiple dosing in practice in Canada, a fact highlighted by Dr. Boobis.[73] Moreover, the EC's own studies confirm that, with most applications, even at doses 10 times the recommended level, residues remain below recommended MRLs,[74] a finding also noted by Dr. Boobis. Thus, even in the unlikely event of inappropriate multiple dosing, the EC's own evidence suggests that residues, for the most part, would remain below safe thresholds.

107. Lastly, in terms of black-market drugs, the EC speculates that the economic incentives for using growth-promoting hormones "cannot exclude the emergence of a black market for less expensive or more effective substances".[75] The EC presents no evidence of illegal use of black-market drugs for growth-promotion purposes in cattle in Canada. Although the EC's own studies reveal that "[i]n the EU dozens of illegal hormones are used",[76] it is not logical to extrapolate the apparent problem with illegal hormone use in countries that outright ban <u>all</u> growth promotants to the North American context where growth promotants are permitted under specific circumstances. Indeed, the very availability of legal growth promotants in North America suggests that the likelihood of the misuse of illegal drugs would be much lower in Canada than in countries that prohibit outright any growth promotants.

108. In conclusion, the EC's claim that it has properly evaluated the potential for adverse effects from the misuse/abuse, a claim contradicted by the experts, does not withstand scrutiny. In addition to being based on several flawed assumptions that do not reflect realistic conditions of use, the assessment simply fails to evaluate the frequency of occurrence of misuse/abuse and the potential

[72] In the Stephany Study, the author suggests that in the EU the mode of application of growth promotants is intramuscular injection (Exhibits EC-49, CDA-12).

[73] Dr. Boobis's reply to Panel Question 62, at pp. 50-51.

[74] Lange, I., *et al*., *Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: Effect of the implant preparations Finaplix-H®, Ralgro®, Synovex-H® and Synovex Plus®* (2001) 109 APMIS 53-65, at pp. 382-383 (Exhibit EC-17).

[75] Commission Draft Report on Assessment of Risks of Abusive Use, at para. 47 (Exhibit EC-73).

[76] Stephany, R., *Hormones found in Meat Samples from Regular Controls in the European Union and from US Imports* (2000) Chemical Awareness: Issue 9, at p. 1 (Exhibit EC-19). Also see the Stephany Study, at p. 358 (Exhibits EC-49, CDA-12).

impact on human health in the unlikely event that misuse occurs. It does not satisfy the requirements for a risk assessment under Article 5.1 and 5.2 as set down by the Appellate Body in the previous Hormones dispute.

(g) Other

109. The EC, in its comments on the experts' responses to **Question 52,** again erroneously characterizes the advice of Dr. Boobis and Dr. Boisseau as based on "assumptions and conservative interpretation", and further that these experts hold the EC's opinion to a higher standard than that to which companies were held when they first received approval for the sale of the hormones as growth promoters.

110. First, the advice from Dr. Boobis and Dr. Boisseau is based on far more than assumptions; it is based on their qualified expertise in their own areas of specialization. The EC may disagree with their advice, but that in itself does not mean it is based on assumptions. If any party in this dispute is making assertions unsupported by the scientific evidence, it is the EC itself, such as with its genotoxicity hypothesis and its reliance on unvalidated measurement methodologies.

111. Second, the EC's accusation that Dr. Boisseau and Dr. Boobis are applying a double standard ignores the history of the evaluation of the safety of these substances. Quite apart from the standard of review to which the original applicants for approval of the hormones were held, the fact remains that the hormones have been repeatedly reviewed and approved by national authorities and international standards bodies, such as Codex and JECFA, on several occasions since the original approval. None of these subsequent reviews, all of which use the latest methodologies and scientific evidence, found that there was any evidence of adverse effects. On the other hand, it is the EC that now claims to have demonstrated that there are adverse effects. It is not only reasonable but legally necessary for the EC to demonstrate, with more than hypothesis and unvalidated methodologies, the potential for the purported adverse effects to occur. Far from being a double standard, this is simply holding the EC to the same standard.

112. The EC also places considerable emphasis on a single statement by Dr. Boobis that the risks from consuming residues in meat from treated animals are "minimal". However, the EC conveniently ignores almost the entirety of the preceding paragraphs in Dr. Boobis's response, in which he states, *inter alia*, that: "none of [the] information provided by the EC demonstrates the potential for adverse effects in humans"; "[t]he studies on genotoxicity provide no convincing evidence of potential for harm in consumers"; "there would be no risk of … [adverse] effects from … exposures" from meat from treated cattle; and "there is no evidence that low level exposure is causing harmful effects in humans" [emphasis added]. Therefore, in light of Dr. Boobis's responses above to the issue of whether the EC has demonstrated the potential for adverse effects, it is quite clear what Dr. Boobis means when he uses the word "minimal".

113. The EC further endorses the responses of Dr. Guttenplan in a manner that is not supported by the advice of the other experts and the comments by the EC itself. The EC cites Dr. Guttenplan's support of the data generated by the Klein RCBA, despite the obvious concerns expressed about these data from all the other experts.[77] The EC then endorses Dr. Guttenplan's favourable reference to the Paris assay data to validate the Klein RCBA data, even though it stated that the former methodology was not appropriate to validate the latter methodology.[78] Finally, the EC cites these statements favourably without acknowledging that Dr. Guttenplan was simply saying that "more accurate methods of analysis could now be used" [emphasis added] to corroborate the EC's concerns, not that in fact they had been used or that the EC's concerns had been corroborated using these methods.

[77] See Canada's comments above, at paras. 89-92.
[78] See EC Comments, Question 38.

114. In its comments on the experts' responses to **Question 53**, it is sufficient to note that in quoting generously the response of Dr. Guttenplan, the EC tellingly failed to address the statement by him that "by far, estrogen is the major agent of risk and, because the concentrations of all the hormones in beef are so low, that they would be unlikely to affect the potency of estrogen". Dr. Boisseau made a very similar statement, which was also tellingly ignored by the EC.

115. The EC's comments on the experts' responses to **Question 54** are confusing and misleading. First, immediately after quoting Dr. Boisseau that the ADI represents the quantity of these residues that can be ingested daily "without causing any problem of health" [emphasis added], the EC concludes that his reply meant that "there is no doubt … that there is a risk", without explaining how the former idea supports the latter conclusion.

116. The EC then misrepresents Dr. Boobis's answer in the same manner when it interprets his statement that the "Codex standard [of no appreciable risk] is equivalent to the EC's stated objective of 'no risk from exposure to unnecessary additional residues…'" to mean that "Codex's standard recognises that there is an [*sic*] scientifically identified risk but recommends its members to follow it…". The EC again leaves unexplained how it justifies going from the former idea to the latter. Indeed, as Canada has explained above,[79] the concept of "no appreciable risk" does not mean that JECFA/Codex have identified some risk, even if minimal; rather, it means that any risk that might exist is purely hypothetical (*i.e.*, not observable). And as the Appellate Body made clear, a risk assessment cannot be based on hypothetical risk.[80]

117. In its comments on the experts' responses to **Question 55**, the EC disagrees with what the experts have to say, so it simply tries to change the subject. Instead of addressing the unanimous advice from the experts that the EC opinions did not evaluate additive risks, the EC chooses to attack the integrity of the experts and the legitimacy of their opinions, and then diverts attention to whether JECFA conducted an evaluation of such risks. The attack on the experts is unjustified: first, because they were asked whether the EC had conducted such an assessment and not whether JECFA did; and second, since it is the EC that claims that there are additive risks, it is up to the EC to demonstrate that such risks exist. In any event, the experts did indicate that JECFA had evaluated additive risks and there were no concerns about such risks arising from meat from treated animals given the extremely low doses of exposure from this source.

118. The EC then acknowledges that the SCVPH did not address additive risks "because the state of scientific knowledge available by then … did not allow such an assessment to be completed". Given that the EC's justification for its bans relates to concerns about proven additive risks, it is nothing short of a remarkable admission that additive risks were not even assessed.

119. The EC provides contradictory comments on the experts' responses to **Question 56**.[81] First, it provides that is has "clearly been shown that the effects from exposure to different estrogens are additive". Then it indicates that it "has tried to do such an assessment [of the additive risks] when the information available was sufficient, but could not complete it because of gaps in our scientific knowledge". Whichever it is, both of these statements are remarkable in light of the importance to the EC's justification of its bans of an assessment of additive risks. And to the extent that the studies cited by the EC say anything about additive risks from oestrogens, they still do not answer the question of whether hormones from meat from treated animals contribute to such additive risks.

[79] See Canada's comments above, at paras. 18-21.
[80] *EC – Hormones*, Report of the Appellate Body, at paras. 199-200.
[81] It is also necessary to note the irony in the EC's criticism of the experts for failing to provide precise references in its answers.

120. In its comments on the experts' responses to **Question 57**, the EC completely ignores the advice of two of the three experts that cast serious doubt on the EC's justification of its authorization of the hormones for therapeutic and zootechnical purposes. In declaring this question unnecessary and irrelevant by virtue of certain Appellate Body findings, the EC completely misses the nature of the experts' criticism of the EC use for these purposes. The issue is not whether there was a violation for authorizing these uses, but that the mere authorization itself undermines the EC's dramatic claims that no threshold for adverse effects from these hormones can be established. This is what leads Dr. Boisseau to call it a "problem of principle" and Dr. Boobis to indicate that this demonstrates the EC believes there is in fact a threshold response. Moreover, the claim that the use of oestradiol for "such purposes is now virtually terminated" does nothing to respond to the criticisms.

121. Since the EC's comments on the experts' responses to **Question 58** merely demonstrate the degree to which its arguments rest on hypothetical situations and assumptions, nothing in its statements warrants further comment from Canada.

122. In commenting on the experts' responses to **Question 59** concerning the EC's non-existent evaluation of the potential for adverse effects on the immune system from residues of hormones consumed in meat from treated animals, the EC employs two diversionary tactics. The first is to indicate that the existing international recommendations that these substances are safe are based on "outdated" data, not on the basis that the data have been superseded, but simply on the basis that they are "old". This line of argument ignores both the fact that the age of the data does not determine their currency and, further, that in any event the hormones have been repeatedly re-evaluated by JECFA as new information becomes available, and the recommendations have remained largely unchanged. The second tactic of course is to argue that it is not the EC that must demonstrate that these adverse effects will occur, but, rather, that it is Canada that must demonstrate that they will not occur. For reasons already discussed on many occasions, this claim is without merit.

123. In its comments on the experts' responses to **Question 60**, the EC comments at great length about the bioavailability of MGA as a feed additive and on the potency of consuming implants of the other five hormones that have not been removed, but in the end provides very little by way of relevant commentary on whether one route of administration leads to adverse effects that are any <u>different</u> from the other route. The EC goes on to challenge Dr. Boobis's comments about the risks from misuse and abuse of MGA implants. However, the EC seems to have understood him to be advising on the implanting of MGA, which is not an approved use, even though it was clear that he was referring to only those hormones that could be administered with implants. To the extent that the EC misunderstood Dr. Boobis's comments, its own comments are of little value.

124. In commenting on the experts' responses to **Question 61** concerning the sufficiency of the evidence to conduct a risk assessment of the other five hormones, the EC does little more than continue its direct attack on the objectivity and professionalism of Dr. Boobis and Dr. Boisseau. The participation in this process of experts that have extensive experience with the evaluations of JECFA of these substances only enhances the Panel's ability to understand the considerable scientific evidence related to the safety of these hormones. Far from lacking objectivity, these experts are best placed to advise the Panel on the sufficiency of the evidence to conduct a risk assessment according to the internationally agreed techniques employed by JECFA. In this case, they both indicated the evidence was sufficient to do so.

125. In commenting on the experts' responses to **Question 62**, the EC continues again its attack, this time singling out the comprehensive and informed review by Dr. Boobis of all of the new material provided by the EC. While the EC indicates that a "more careful examination by a real expert of the same body of evidence" led to the opposite conclusions to those offered by Dr. Boobis, it neglects to inform the Panel and Canada who this "real expert" is and why his or her anonymous views should be considered more authoritative that those offered by the expert specifically chosen for

the task. In any event, it is difficult to see how the EC could consider Dr. Guttenplan's one paragraph enumeration of gaps a "more considered and objective view" than the 11 pages of analysis offered by Dr. Boobis.

III. COMMENTS ON THE COMMENTS FROM THE EC ON THE RESPONSES FROM THE INTERNATIONAL BODIES

126. In relation to the EC's comments on the responses by the international bodies to **Questions 1**, **5, 16**, **17**, **18** and **19**, Canada will not comment at this time.

127. In relation to the EC's comments on **Questions 3** and **4,** Canada refers to paragraphs 12-14 of this document.

128. In relation to **Question 7,** Canada refers to paragraphs 23, 35-44, and 83-92 of this document.

129. In relation to **Question 8,** Canada refers to paragraphs 35-44 of this document.

130. In relation to **Question 9,** Canada refers to paragraphs 18-21 of this document.

131. In relation to **Question 10,** Canada refers to paragraphs 12-14, 83-92, 116-118 of this document.

132. In relation to **Question 11,** Canada refers to paragraph 77 of this document.

133. In relation to **Question 12,** Canada refers to paragraphs 16 and 17, 18-21 of this document.

134. In relation to **Question 13**, Canada refers to paragraph 77 of this document.

135. In relation to **Question 14,** Canada refers to paragraph 5 of this document.

136. In its comments on the responses **Question 15**, the EC continues to ignore the existence of the *Recommended International Code of Practice for Control of the Use of Veterinary Drugs*, of Codex, which was mentioned by Codex as well as Dr. de Brabander.

137. In relation to **Question 20**, despite the explanation by JECFA that the three natural hormones had been placed on the agenda of JECFA in 1999 at the initiative of the JECFA Secretariat to ensure that all the latest information had been evaluated, the EC insists that, in its words, "most of the data were the same old data". The Panel may wish to ask JECFA for further clarification in this regard. Canada also refers to paragraph 77 of this document.

138. In relation to **Questions 23, 24, 25** and **26**, Canada refers to paragraphs 29-34 of this document.

IV. CONCLUDING COMMENTS

139. As the above comments demonstrate, rather than address specifically many of the important concerns raised by the experts about the EC's evaluation of the safety of the hormones, the EC has chosen instead to attempt to create confusion about these issues. It has done so by presenting the responses of experts in a misleading and flawed manner; it has done so by misrepresenting the meaning of much of the scientific evidence and international guidance documents; and it has done so by attacking the professionalism and objectivity of the experts and the Secretariats of the international organisations.

140. Canada is confident, however, that the Panel will see through these efforts and will keep the focus on the real issues, and on the legitimate scientific and technical material, on which it needs advice to decide this case. Ultimately, on the basis of the substance of the responses from the experts and the lack of substance in the comments by the EC, Canada is confident that the experts have provided sufficient advice to allow the Panel to conclude that the EC's bans are not justified by the scientific evidence.

WORLD TRADE ORGANIZATION

WT/DS321/R/Add.7
31 March 2008

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CANADA – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex G to the Report of the Panel to be found in document WT/DS321/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex B: Add.2
- Annex C: Add.3
- Annex D: Add.4
- Annex E: Add.5
- Annex F: Add.6

ANNEX G

TRANSCRIPT OF THE PANEL'S JOINT MEETING WITH SCIENTIFIC EXPERTS ON 27-28 SEPTEMBER 2006

27 September 2006, morning

Chairman

1. Good morning. I would like to welcome the parties, the Panel's experts and representatives of international organizations to this joint meeting of the two Panels; the Panel on *United States – Continued Suspension of Obligations in the EC Hormones Dispute*, referred to as WT/DS320, and the Panel on *Canada – Continued Suspension of Obligations in the EC Hormones Dispute*, referred to as WT/DS321. The experts with us today are Dr. Boisseau, Professor Boobis, Dr. Cogliano, Professor De Brabander, Professor Guttenplan and Professor Sippell. We have representatives from the secretariats of the three international institutions: the Codex Alimentarius Commission, the Joint FAO/WHO Expert Committee on Food Additives, known as JECFA, and the International Agency for Research on Cancer, known as IARC. The representatives are Dr. Angelika Tritscher, WHO JECFA Secretary, and Dr. Annika Wennberg, FAO JECFA Secretary, Dr. Kazuaki Miyagishima, Codex Secretary, and Dr. Cogliano, one of the Panel six experts, who is also head of the IARC's Carcinogen Identification and Evaluation Group.

2. May I now invite the heads of delegations of each party to introduce themselves and the other members of their delegations. I would appreciate if you could submit the list of your delegations' members to the Panel secretary if you have not done this already. The European Communities first please.

European Communities

3. Good morning. My name is Theofanis Christoforou. I am Principal Legal Advisor of the European Commission in Brussels and I will be functioning as the head of delegation for these two days. If you agree each member of the delegation will introduce himself or herself.

4. Good morning. My name is Thomas Jürgensen – I work for the European Commission.

5. Good morning. My name is Sybilla Fries. I am from the Legal Service of the European Commission, now based in Geneva.

6. Good morning Chair. My name is Gudrun Gallhoff. I work for the European Commission Directorate General Health and Consumer Protection.

7. Good morning. Brian Marchant of the Commission, working for DG Trade.

8. Good morning. Lothar Ehring, European Commission, DG Trade.

9. Good morning. My name is Lars Berner and I am with the EC delegation here in Geneva.

10. Gentlemen, this was the delegation as such, the officials, lawyers and other advisors. Now we have a long list of experts with us and will also allow each one of them to present themselves, starting from Mr. Dan Sheehan.

11. Daniel Sheehan from Daniel M. Sheehan & Associates.

12. Annie Sasco from the University of Bordeaux, cancer epidemiologist.

13. Manfred Metzler, Professor of Food Chemistry, University of Karlsruhe, Germany.

14. Niels Skakkebaek, Medical Professor, Growth and Reproduction, Copenhagen University.

15. Henrik Leffers, Microbiologist, Growth and Reproduction, Copenhagen.

16. Professor François Andre from the National Veterinary School of Nantes, National Reference Laboratory for Hormones, Ministry of Agriculture.

17. Alain Paris from National Institute for Agronomic Research. I specialize in metabolism of steroids.

18. Professor Heinrich Meyer, Technical University of Munich. I am the Chair of biochemistry and physiology at the Technical University. Thank you.

19. I am Professor Frederik Vom Saal of the University of Columbia, Missouri in the United States.

20. With the delegation are also representatives of the member States of the European Community, and if you agree they will present themselves. Thank you.

21. Jukka Pesola, Counsellor, Permanent Commission of Finland.

22. I am Christian Forwick from the German Mission in Geneva.

23. I am Sebastian Keyserlingk from the German Ministry of Agriculture.

24. I am Anders Christiansen from the Danish Mission, Geneva.

25. Luca Burmeister, Danish Mission to Geneva.

26. Lukas Paul from the German Mission here in Geneva.

27. Cédric Pène from the French delegation in Geneva.

28. Blas Vicente, Spanish Mission in Geneva

Chairman

29. Thank you. The United States please.

United States

30. Good morning Mr. Chairman, members of the Panel. My name is Jay Taylor with the US Trade Representative's Office. To my left is Dan Hunter with the US Trade Representative's Office here in Geneva. To my right is Dr. Adele Turzillo with the Food and Drug Administration. To Adele's right is Steve Wolfson with the Environmental Protection Agency. To his right is Kelly Stange with the Foreign Agricultural Service. To her right is George York with the US Trade Representative's Office here in Geneva. Across the table from George is Dr. Ralph Cooper with the Environmental Protection Agency. Next to Dr. Cooper is Rita Kishore with the US Department of Agriculture Food Safety and Inspection Service. Next to Rita is Dr. Richard Ellis, Consultant,

formerly of the Food and Drug Administration. And next to Richard is Dr. Gregg Claycamp with the Food and Drug Administration. Thank you.

Chairman

31. Then I give the floor to Canada.

Canada

32. Thank you Mr. Chairman. I am Rambod Behboodi, First Secretary here at the Canadian Commission to the WTO. Counsel with me today who will argue this case are to my left Mr. Rob McDougall at the Trade Law Bureau, and to my right Mr. Kevin Thompson, also of the Trade Law Bureau of the Department of Foreign Affairs and International Trade. The rest of the members of the delegation, from the far left, there is Angela Webb who is the Paralegal, Dr. Don Grant who is adviser to the Government of Canada. Next to Mr. Thompson we have Dr. Jim MacNeil who is head of the Centre for Veterinary Drug Residues of the Canadian Food Inspection Agency. We also have Ms. Michele Cooper, First Secretary at the Canadian Mission and Mr. Vasken Khabayan, who is Second Secretary at the Canadian Mission, and across from me Mr. Evan Lewis of the Technical Barriers and Regulations Divisions of the Department of Foreign Affairs and International Trade, and Mr. Bill Bryson of the Department of Agriculture. Thank you.

Chairman

33. Thank you. I would like to continue by introducing the members of the Panels. On my right is Ambassador William Ehlers, who is Ambassador of Uruguay to India. On my left is Madam Claudia Orozco, who is a former senior official of the Colombian Government and who is now working in Brussels as an independent consultant. And myself, Tae-yul Cho, serving as Chair of these Panels. I am Ambassador and Deputy Representative in the Korean Mission here in Geneva. The two Panels are composed of the same individuals and in agreement with the parties, we are holding a joint meeting with the experts consulted by the Panels.

34. I would also like to introduce the Secretariat officials who will be assisting the Panel: Mr. Yves Renouf, Legal Officer to the Panel; Ms Xuewei Feng, Secretary to the Panel, and Ms Gretchen Stanton, Ms Serra Ayral and Ms Christiane Wolff from the Agriculture and Commodities Division of the WTO Secretariat. Finally I would like to inform the parties of the presence of Mr. Walters Nsoh, Intern in the Agriculture Division and Ms Esther Katende, an intern with the WTO Legal Affairs Division.

35. As you all know, further to the parties' common request, the Panel has decided to hold this meeting with the experts open for observation by the public through a closed circuit TV broadcast. I would also welcome those who are observing this meeting from another room at this moment. I would like to remind the viewers who are observing this Panel meeting that tape-recording or filming during the Panel meetings by anyone other than the WTO Secretariat is not permitted. In order to ensure an orderly proceeding and as a courtesy to everyone, I also request everybody, including those participating in the Panel meeting and those observing the meeting of the Panel, to turn off their mobile phones during the whole meeting.

36. In addition I would like to underline that the parties may request that the public microphones be switched off when any confidential material or information is being discussed. Finally, if the meeting is adjourned or suspended, I will specify the time at which it will resume for the benefit of those in this room, but also for those viewing this hearing from CR II.

37. May I also remind you that the meetings of panels in the WTO are tape-recorded and that at today's meeting as well as the meeting of tomorrow, English/Spanish/French simultaneous interpretation will be provided in relation to the public broadcast of this hearing through closed circuit television into Room CR II at the request of the parties. So please be sure to use the microphones when addressing the Panel and above all, speak slowly. I would like to express my sympathy with the interpreters for this meeting considering its extremely technical nature. I would also like to remind the experts and the parties that there are constraints and difficulties of interpretation and therefore technical language will be properly interpreted only if it is delivered at the reasonable pace. To the extent possible, any prepared notes or statements should be shared with the interpreters so as to facilitate their task and ensure accurate interpretation.

38. Turning to a brief history of the Panels' proceedings, I wish to recall that at its meeting of 17 February last year the Dispute Settlement Body decided in accordance with Article 6 of the Dispute Settlement Understanding to establish two Panels pursuant to requests of the European Communities. I further recall that the Panels held a joint first substantive meeting with the parties and third parties on 12-15 September 2005.

39. After its first substantive meeting, the Panel decided on 20 October last year to consult with experts who have specialized scientific expertise on the issue arising in this dispute. In consultation with the parties, the Panel adopted working procedures for its consultations with scientific and technical experts. These working procedures were communicated to the parties on 25 November 2005.

40. The Panel received suggestions from experts from three international organizations, namely, the Codex Alimentarius Commission, the Joint FAO/WHO Expert Committee on Food Additives, the IARC, and from the parties. Following consultations with the parties on the candidate experts, the Panel appointed, as I mentioned, Dr. Boisseau, Professor Boobis, Dr. Cogliano, Professor De Brabander, Professor Guttenplan and Professor Sippell to serve as scientific experts in this dispute.

41. In accordance with working procedures and after having considered the parties' comments, the Panel sent questions to the experts and international organizations on 13 April this year. The experts were requested to reply in writing by 12 June 2006, and these replies were communicated to the parties. Comments and counter-comments received from the parties and the expert replies were also provided to the experts in July.

42. The purpose of today's meeting is for the Panel to obtain further clarification of the scientific issues and to discuss the experts' written responses to the questions. The parties will also be given an opportunity to discuss the responses of the experts to the questions.

43. This two-day meeting will proceed in the following manner. Before proceeding with an examination of the specific scientific issues under consideration, the Panel will first give an opportunity to each expert and international organization representative to introduce themselves and make some brief introductory remarks, in particular in light of parties' written comments on their specific responses to these questions. But please bear in mind that these remarks should be kept as general as possible since we will subsequently discuss each issue in more detail.

44. Afterwards, the Panel intends to hold its discussions under five areas which are linked closely with the specific sections included in the written questions of the Panel to the experts. I will clarify the specific areas in a moment. For each of the five specific areas, I will open the floor to the parties to ask questions to the experts based on the written information and comments received thus far, addressed either to a specific expert or to the experts in general. The Panel would also pose some questions either at the beginning or following parties questions, depending on the issue. Once the question and answer process has been completed for one area, I will invite the experts and

international organization representatives to make some concluding remarks, if they so wish, before moving on to next area. In addition to the four predetermined areas, we have also foreseen a fifth area to address any other issues not covered by any of the four areas.

45. Concerning the questions by the parties to the experts, the Panel will proceed as follows. Under each section, the Panel will first give the European Communities the floor to ask questions to the experts. Thereafter, the United States and Canada will be given an opportunity to ask their questions to the experts, including any follow-up questions to those posed by the European Communities. After that, the European Communities will be given the opportunity to pose any follow-up questions to those posed by the US and Canada. The Panel is mindful that these are officially two proceedings and it will make sure that parties are given ample opportunities to ask questions necessary for a clear understanding of the facts. However, the Panel notes that the scientific issues are similar in both cases and would strongly encourage the parties to avoid duplicating questions. Please all keep in mind that this meeting has been convened primarily to hear the views of the experts and that parties will have ample opportunities to express their views at our meeting next week.

46. Finally, once we have covered all the five specific sections, I would like to give each expert and international organization representatives an opportunity to make concluding remarks based on the discussions held by that time. I am not intending to invite parties to make any concluding remarks during this meeting since they will have the chance to discuss any relevant points further during the Panel's second substantive meeting with parties scheduled for next Monday and Tuesday.

47. I would like to underline that the Panel may ask follow-up questions at any time during the proceedings. Moreover, although the Panel or the parties may address a question to one or more specific experts, all experts should feel free to respond to specific questions if they so wish. In making any remarks, both parties and experts are requested to minimize redundancy with what they have already submitted to the Panel in writing. I would also like to remind you all that experts and international organization representatives are expected to answer scientific and technical questions; they must refrain from addressing any legal issues, such as questions of interpretation of the SPS Agreement.

48. I would also like to recall that the purpose of today's meeting is to take advantage of the experts' presence to allow the Panel to gain a better understanding of the scientific issues before us. The Panel's experts have been selected after extensive consultations. I would like to express the Panel's appreciation for their contributions and their presence today. I am confident that the parties will also make the best of their expertise during these two days.

49. Let me also clarify that the Secretariat staff will prepare a summary of all the information provided by the experts and international organizations in their written responses to the questions as well as a transcript of the information provided by the experts and international organization representatives in the meeting today and tomorrow. Each expert will be asked to review this summary and the transcript and to confirm its accuracy. These will be part of the Panel's reports on these disputes.

50. Last but not least, I would like to recall that we the Panel members do not have scientific expertise. Therefore I would like to ask the experts to bear this in mind in replying to questions and explain issues in layman's terms, providing information on underlying concepts as necessary. In order to get a clearer picture with respect to the six hormones at issue, I would also like to invite all those taking the floor to clarify which of the six hormones their question or reply applies to.

51. Now I would like to introduce the five areas that I referred to earlier. In order to facilitate a focussed discussion, the Panel would like to structure the meeting under four specific areas which

relate to the Panel's original written questions: Area 1 relates to terms and definitions, which corresponds mainly to Section A of the Panel's written questions to experts; Area 2 is risk assessment techniques, which corresponds roughly to Section B of the Panel's questions and to some of the Panel's questions to international organizations; Area 3 is related to relevant scientific evidence, which corresponds roughly to Section D of the Panel's questions to experts; Area 4 relates to EC assessment of risks, corresponding roughly to Section C and some elements of Section D of the Panel's questions; and Area 5 is, as I mentioned, other – any follow-up questions that do not fit in the above categories.

52. In their replies, the experts may want to refer to various documents, including the parties' submissions and exhibits. These documents are either filed in the binders placed in the cupboard over there, or in the CD-Roms. The CD-Roms can be opened and viewed in the laptop computers near your seats. The Secretariat staff are ready to help you locate these documents if necessary.

53. Unless there are any comments or questions we can now proceed to hear the experts' brief introductory remarks. I will first give experts the floor in an alphabetic order, starting with Dr. Boisseau, which will be followed by the representatives of the international organizations. Dr. Boisseau, you have the floor.

Dr. Boisseau

54. Thank you, Mr. Chairman. Let me begin by apologizing for my voice – I caught a cold some time ago and I am afraid that my voice is not very clear, but I shall do my best to make myself understood. So, my name is Jacques Boisseau, and I withdrew from professional life four years ago. Before that, I directed the National Agency for Veterinary Medicinal Products (ANMAV) in France for 20 years. I was a member of the European Union's Committee for Veterinary Medicinal Products for 14 years and headed it for six years when it was still in Brussels. For 13 years I participated in all of the meetings of the JECFA, and had the honour to chair four of them and to be Vice-Chairman five times. Finally, for about 15 years I headed the French delegation to the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF). So, I specified in my curriculum vitae that in the above capacities, I had not done any scientific work on hormones, and that consequently, I had not published anything on the subject. I suppose that I have the honour to be part of this panel of experts thanks to my experience in assessing the safety of residues of veterinary drugs in food. I would like at this point to make three remarks that could be of help to the discussions that will be taking place over these two days.

55. The first comment is as follows: the experts have been given 64 precise questions, to which they were asked to provide precise answers. Consequently, I think that any comments on the replies of the experts, or criticism thereof, should focus on the replies in relation to the questions asked and not in relation to the questions that were not asked. Secondly, I think it is important that we should all have a common understanding of the risk analysis procedure. In other words, we should clarify together, and in agreement with each other, what pertains to the risk assessment procedure as opposed to the risk management procedure. We should be able, as well, to reach a common understanding of what a hazard is, and what a risk is. Finally, we should be able to adopt a common approach to what a qualitative risk assessment, is as opposed to what we might call a quantitative risk assessment. Finally – since I had meant to be brief – I think that we must clarify together the specificities of conducting a risk analysis for an endogenous substance as opposed to a risk analysis for xenobiotic substances. There we are, Mr. Chairman, thank you very much.

Chairman

56. Thank you. Professor Boobis, please.

Dr. Boobis

57. Thank you Mr. Chairman. My name is Alan Boobis. I am currently a professor of biochemical pharmacology at Imperial College London where I am also a director of the Department of Health Toxicology Unit. I originally trained in pharmacology at the University of Glasgow, but since 1976 have been involved in studies of xenobiotic metabolism of foreign compounds and in toxicology, particularly mechanisms of carcinogenesis of dietary contaminants. For the last 15 years I have played a role in national, regional and international advisory committees, as an independent member of a number of committees advising on the safety of chemicals, both pesticides, veterinary drugs and consumer products. I have published over 200 papers in peer reviewed journals, including a small number on issues of hormone research. I currently have two PhD students and a post-doctorate research fellow working on aspects of oestrogen toxicity.

58. I have very few comments to make specifically about the issue at hand today because I hold myself ready to expand upon my responses to the questions. I would just make one general comment at this time which is that in risk assessment it is important to recognize that it is not possible to establish safety with absolute certainty. Safety is a concept which is related to the probability of harm, and this is the reason that we use terms like "no appreciable risk". In risk assessment we don't have a concept of zero risk, because in strict scientific terms of risk assessment, risk is considered as a probability – the probability of harm based on the hazard of the compound and the specific conditions of exposure to the agent under consideration. Thank you.

Chairman

59. Thank you. Dr. Cogliano, please.

Dr. Cogliano

60. Thank you, Mr. Chairman, members of the Panel. My name is Vincent Cogliano. I am the Head of the IARC Monographs Programme at the International Agency for Research on Cancer in Lyon, France. The IARC monographs are a system of expert scientific reviews where we convene international working groups of scientific experts to evaluate the potential carcinogenicity of a variety of agents. They started out looking at chemical agents but since then have evolved to look at occupational exposures, chemical mixtures, lifestyle factors, physical and biological agents. Over the 35 year history of the Monographs Programme we have looked at over 900 agents and identified approximately 400 as potentially carcinogenic to humans, including 100 agents which are considered to be known to cause cancer in humans.

61. I am here perhaps in a double role; partially in my role at the International Agency for Research on Cancer but also as a member of the expert committee. Before coming to IARC I worked for nearly 20 years at the United States Environmental Protection Agency in Washington, DC where I was part of the Office of Research and Development assessing the health hazards of chemicals found in the environment. I am not going to make at this time any particular statements about risk assessment or risk but I do stand ready to assist the Panel in any way I can in answering any questions that come up today. Thank you.

Chairman

62. Thank you. Then I will give the floor to Professor De Brabander. Please.

Dr. De Brabander

63. Thank you, Mr. Chairman. My name is Hubert De Brabander. I know that my name is difficult to pronounce for non-Dutch speaking people, but we'll do our best. Maybe you can give me a nickname or something if you want to address me. I am from Belgium, from Ghent University, from the Faculty of Veterinary Medicine. I am trained as a chemist and during my PhD in chemistry I also obtained a degree in environmental chemistry, and concern for the environment will stay with me for the rest of my life. Then I was offered a position at the Faculty of Veterinary Medicine and I am still there as Head of Department of the Department of Veterinary Public Health and Food Safety. Over the years I worked mostly on analytical chemistry, residue analysis. I did a second PhD in analytical chemistry of food (aggregaat hoger onderwijs) and also a PhD in veterinary sciences. As you see my background is in analytical chemistry, but over the years I have become a little bit "veterinized", I should say. What I can offer to the Panel is my background, my experiences with residue analysis and practical experience in control of legal and illegal compounds. Thank you.

Chairman

64. Thank you. Professor Guttenplan.

Dr. Guttenplan

65. My name is Dr. Guttenplan. I have a PhD in chemistry but I have been working in biochemistry and carcinogenesis for over 30 years. I also have a Masters in public health and environmental sciences. I have been teaching biochemistry for a number of years and have been involved in carcinogenesis for 30 years. In responding to the questions I found one of the most difficult points to evaluate was the word "potential". Many times it arose – this is a potential carcinogen, this is a potential hazard – and this comes back to the notion of risk; almost any chemical can be toxic if the dose is high enough. I think this has been a very difficult area for the Panel to determine; what a dangerous dose is, and whether the doses of hormones that are in the cattle produce levels in humans that are dangerous. I am prepared to answer any questions during my responses throughout the day. Thank you.

Chairman

66. Thank you. Professor Sippell, please.

Dr. Sippell

67. Thank you, Mr. Chairman. I have prepared for introduction a few PowerPoint slides.[1] (May I have the first one.) Yes, there you see my affiliation; I am the only one of the experts who is a medical doctor, more specifically a Professor of Paediatrics, and I have been running the Division of Paediatric Endocrinology and Diabetology for now more than 25 years and also running a relatively highly-developed paediatric endocrinology lab. Our speciality is to do refined steroid analysis in very small samples from children, from premature babies to adult individuals.

68. (Next – just the first line of the second slide please.) I am a relative newcomer in the field and it is very interesting that this dispute has already been going on for more than a decade, and to my knowledge no paediatrician, let alone a paediatric endocrinologist, has been involved as a member of one of your expert committees. To my knowledge, neither has one of the very active scientific organizations been involved in these disputes, for example the Lawson Wilkins Paediatric Endocrine Society which serves North America, so not only United States but also Canada, or the European

[1] Dr. Sippell's slides are contained in Attachment 1 to this transcript.

Society for Paediatric Endocrinology. This fact is incomprehensible and paradoxical in view of the fact that prepubertal children are indisputably the most sensitive and vulnerable members of the population.

69. (Next point, yes, you can leave it there.) Children have the smallest body size but the longest life expectancy and I see (next please) my mission here as an advocate of and spokesperson for children and their specific needs. Just remember that children are not just small adults but something very special and they are our future, no doubt. Through my reading (can you go on) I got the impression that the validity of the supersensitive recombinant cell bioassay for oestradiol is a key issue in all the debate at stake. I would like to remind you that this supersensitive assay has been developed at the National Institutes of Health, the foremost and most refined research institution of the United States. And with our American colleagues – who in general really don't question the validity of this assay (can you go on please) the novel finding of significantly higher oestradiol levels – E2 stands for oestradiol, the female sexual steroid – in prepubertal girls than in boys readily explains fundamental features of human biology for the first time. Many questions that had not been answered before, basic biological questions, can be answered now by this quantum leap supersensitive assay of oestradiol in small biological samples. So for instance, the onset of puberty is on average one year earlier in girls than in boys. This is readily explained by a higher oestrogen input in girls endogenously, from the ovaries, which are not sleeping during pre-puberty but are active on a low level. The second aspect is the much faster bone maturation in girls than in boys, with a result that bone maturation is ready in girls on average at age 15, whereas it is mature at age 17 in boys.

70. (Next point.) Lower adult height in women than in men by a mean of 13 centimetres – in all populations men are taller than women. This can only be explained by this higher prepubertal oestrogen secretion in girls than in boys. (Next.) The higher weight for height or body mass index in girls than in boys at start of normal puberty is also readily explained by this. We have evidence that oestrogen exposure increases weight, and you can see in the next slide a piece of our own research. You can see on the left-hand side in the yellow box plot were 50 girls with central precocious puberty, in some of them puberty started at age two already, and at diagnosis they were already two standard deviations in weight above the mean for age and sex. So oestrogen exposure – in these cases endogenous oestrogen supersecretion – leads to increased weight. And we have shown that treatment of this disorder does not increase weight – you can see that the BMI standard deviation score stays stable or goes down.

71. (Next please, and I am coming to the end.) The incidence of central precocious puberty, as I told you, is about 10 times higher in girls than in boys. This is only explained by the fact that girls have prepubertally higher levels of oestrogen than boys. (Next.) I contrast, the incidence of constitutional delay of puberty is much more common in boys than in girls.

72. (And then the last slide.) Ethical considerations – they should always be kept in mind. To investigate whether eating hormone-treated beef elevates oestrogen levels in prepubertal children, tests cannot be performed in healthy children, because this would involve physical and psychological injury to them. (And the next.) Epidemiological studies comparing adverse effects in mass populations – and I have read in some of the comments that this is advocated – in healthy children eating beef from hormone-treated and untreated animals to compare them would also be unethical. We have to protect children from unnecessary clinical trials. This is not only (can you go on) written in the Declaration of Helsinki, but also in all good clinical practice guidelines and in the recent EU Parliament ruling on better medicines for children. I thank you for your attention.

Chairman

73. Thank you. I now request Dr. Miyagishima, the Codex representative, to take the floor.

Dr. Miyagishima

74. Thank you, Mr. Chairman, and I thank all the members of the Panel for having given the opportunity to the Secretariat of the Codex Alimentarius Commission to be invited to this Panel hearing. The Codex Alimentarius Commission is one of the three international standards-setting bodies explicitly enumerated in Annex A of the SPS Agreement. The Codex Alimentarius Commission was established in the early 1960s by FAO and WHO as an intergovernmental body operating under the auspices of these two parent organizations. The core business of Codex is to set international food standards and other related texts with the objective of protecting the health of consumers and ensuring fair practices in food trade. Codex, by setting international standards, acts as an international risk-management body, if I put it in the overall framework of risk analysis. Codex, as such, does not undertake any risk assessments but draws on the work done by FAO/WHO scientific bodies in that respect. The membership of the Codex Alimentarius Commission is open to all member states of FAO or WHO. Currently the Codex membership counts 174 countries, thus covering more or less 99 per cent of the world's population. Codex has one member organization, the European Community, which made a formal accession to Codex in November 2003. Codex' highest decision-making body is the Codex Alimentarius Commission, which used to meet every year after the creation of Codex, then the Commission turned to a biennial meeting rhythm, and since 2003 the Commission is again meeting every year.

75. The Commission adopts the final draft standards prepared by its subsidiary bodies, and Codex has 20-plus subsidiary bodies covering distinct speciality fields. In the 1980s, Codex decided to extend its activity area to cover the residues of veterinary drugs in food. Codex thus established the Codex Committee on Residues of Veterinary Drugs in Foods, known as CCRVDF. This Committee met for the first time in 1986 and continued to meet yearly until 1992; since then it is meeting more or less at the interval of 18 months. CCRVDF acts as a subsidiary body of the Codex Alimentarius Commission on matters related to the residues of veterinary drugs in food, and as mentioned earlier it does not conduct any risk assessments. It bases all recommendations that this Committee forwards to the Commission on the scientific advice given by JECFA. Of course JECFA covers a broader field than just the question of residues of veterinary drugs; it also covers food additives and contaminants and as such advises other subsidiary bodies of the Codex Alimentarius Commission.

76. Mr. Chairman, this is a brief outline of the history and the mission of the Codex Alimentarius Commission, and I am willing to provide further clarification or supplementary information with regard to the written information we have provided. I would like to stress the fact that we represent – together with the joint secretaries of JECFA – our respective organs and we do not, in my case, represent directly the member states. I would be most happy to reply on questions regarding procedures and facts, but I am rather reluctant to make any comments on those questions requiring value judgements or any analysis or assessment of scientific data. Thank you, Mr. Chairman.

Chairman

77. Thank you. May I now invite the JECFA representatives, Dr. Tritscher and Dr. Wennberg, to take the floor in turn and to make their introductory remarks.

Dr. Tritscher

78. Thank you, Mr. Chair. My name is Angelika Tritscher; I am from the World Health Organization here in Geneva. And within the WHO I work in the International Programme on Chemical Safety. Within the Programme I am responsible for the Chemicals in Food Programme. The main part of this Chemicals in Food Programme is to be the scientific secretariat to international expert bodies that perform risk assessment on chemical residues in food. We have two expert bodies, JECFA and JMPR. JMPR is the Joint Meeting on Pesticides Residues, but it is not of relevance here.

The other expert body, as already mentioned, is the Joint Expert Committee on Food Additives, which despite the name, as was already alluded to, deals not only with food additives but also with contaminants, natural toxins and veterinary drug residues in food.

79. Very brief to my training: I myself trained in food science – I have a Masters degree in food science and a PhD in biochemical toxicology. However, as was already mentioned, I am not here in a role as a scientific expert. My role here in this Panel is to explain JECFA procedures and risk assessment methodologies and definitions as scientific secretary to the committee.

80. Let me say a few words about JECFA, to explain what JECFA is. JECFA is an international independent scientific expert body. It is jointly administered by FAO and WHO. It is not a standing committee, so JECFA experts are invited for each meeting, depending on the compounds on the agenda and the tasks at hand. As was already explained, in the international arena of food safety, JECFA is the risk assessment body and does not deal by any means with risk management activities, which in the international arena are the responsibilities of Codex and its subsidiary bodies. As mentioned, JECFA is jointly administered by FAO and WHO, and FAO and WHO have complementary roles in administering this Committee and inviting respective experts. The role of the WHO secretariat, according to the role of the WHO, is to invite experts that perform toxicological evaluation of the available data and then together with FAO – and my colleagues from the FAO secretariat will explain in more detail the role of FAO and FAO experts overall – the risk assessment is performed. The WHO experts perform the toxicological evaluation.

81. JECFA first met 50 years ago – the first meeting was in 1956 – which means JECFA predates not only me but also the Codex Alimentarius Commission. Over the years, JECFA has really laid the ground work by developing the principles for how risk assessment of chemicals in food is done nowadays, both on the international and on national levels. Besides laying the groundwork, there is continuous improvement over the years, as published in the reports of each JECFA meeting. All publications of JECFA are publicly available, which nowadays luckily means on the internet, but also in print. We publish reports of each meeting that give the precise description of the data that allow the conclusion. Then we have toxicological monographs, published in the WHO Food Additives Series, that give a detailed description of the full toxicological database, including the full reference list. So far to the transparency of the outcome of the JECFA procedures. I will be glad to answer any questions there may be regarding JECFA procedures, in particular risk assessment methodologies and so forth. And with this I would like to give over to my colleague from the FAO. Thank you.

Dr. Wennberg

82. Thank you, Mr. Chairman. My name is Annika Wennberg, and as was said by my colleague Dr. Tritscher, I am the FAO JECFA Secretary. We work together; we have complementary roles to serve JECFA as the independent scientific committee in international settings. As was also mentioned, JECFA has been in place for some time, since 1956, and it actually started to evaluate veterinary drugs in 1987. The first meeting dedicated to veterinary drugs residues was held in 1987, and JECFA also started developing the general principles for the assessment of residues in veterinary drugs in food. Under the FAO constitution, JECFA is convened according to article 6, which lays down that the Conference of the Council of FAO may establish committees and working parties to study and report on matters pertaining to the purpose of the organization. These consist of individuals appointed in their personal capacity, because of their special competence in technical matters. Joint committees may also be established according to that article. This is the basis for the support of FAO to the work of JECFA.

83. I myself have a PhD in nutrition and metabolism from the medical faculty of Gothenburg in Sweden. I have also been involved in evaluations of veterinary drugs in my previous position as employee of the Medical Products Agency in Sweden. But I am here in my role as the JECFA

Secretary to respond to questions and clarifications that may be asked about the procedures and the principles of JECFA, not to respond to any questions on the substance matters. Thank you for inviting me and I will stop here.

Chairman

84. Thank you all for your introductory remarks and particularly for their brevity. I think that concludes our introductory part of this morning's session, and I now turn to the main business of today, the consideration of specific issues in the five areas I mentioned. On the first area I would like to let you know that the Panel would first like to pose some questions related to certain terms and concepts and definitions. I will pose our questions one by one, and after listening to the replies from the experts and from the parties, I will move on to the next question.

85. The Panel's first question is: Please explain the terms genotoxic, mutagenic and carcinogenic. How are they related? How do they differ? What are the consequences if a substance is genotoxic, mutagenic and/or carcinogenic? I would welcome any replies from any of the experts present, please.

Dr. Guttenplan

86. A genotoxic substance is one which damages DNA. Many genotoxic substances are mutagenic and many genotoxic substances are carcinogenic. Whether they pose a risk depends on the dose.

Chairman

87. Dr. Boobis.

Dr. Boobis

88. Just a further clarification of some of these terms. A carcinogenic compound is one that causes some abnormality of growth control and results in a tumour. It can arise from many different mechanisms. One of them is through direct damage to DNA, which is genotoxicity, and mutagenicity is a change in the sequence of the DNA caused by a genotoxin. So there are several different mechanisms of genotoxicity, some of them due to direct interaction with DNA.

Chairman

89. My colleagues asked if you could speak a bit more slowly.

Dr. Boobis

90. So there are many different mechanisms of genotoxicity, for example one can interfere with the mitotic spindle, which is the apparatus that determines how cells divide, or there could be direct modification of the DNA, which could lead to a mutation, a heritable change in the DNA. These mechanisms can give rise to cancer, but there are other possibilities, such as a mitogenic stimulus, something that stimulates the cells to divide. Perhaps random errors during normal replication can lead to the selection of cells which have a tumorigenic potential and could grow into a tumour. It is critical therefore in the risk assessment of something which produces cancer in an animal – which is simply a descriptive term, that is that we observe a tumour in an animal – that if possible we would determine the mode of action or mechanism leading to those tumours; and if the compound is shown to cause genotoxicity, if possible to determine how that compound caused genotoxicity. Not all genotoxicity is the same, because some of it is direct and some of it is indirect.

Chairman

91. Thank you. I am wondering whether any of our colleagues in the Panel have …

European Communities

92. Thank you, Chairman. Would you allow me to ask a clarifying question? The question is to the two scientists that have already expressed themselves, I think in particularly to Dr. Boobis. Dr. Boobis, in reply to question number two you have stated regarding genotoxic potential that the compound might be capable of causing genotoxicity, and then you say usually *in vivo*. You continue then to say it remains to be determined whether genotoxicity is indeed expressed *in vivo*. So there are a few words and each word of course changes specific meanings and significance. The question is, do we always need to find genotoxicity *in vivo*? Is it sometimes sufficient that we observe in large numbers of experiments genotoxicity *in vitro*, and are there examples of substances for which we have accepted that they are genotoxic on the basis of the large number of experiments *in vitro*? I don't quite understand what you mean, it remains to be determined whether genotoxicity is indeed expressed *in vivo*. Could you please elaborate and eventually …

Chairman

93. Before I give the floor to Dr. Boobis, may I remind the delegations that we will have further opportunities to exchange our discussions on the specific issues relating to risk assessment techniques and so on. So why don't you confine your questions to the terms and definitions at this moment, and then I will move on to the discussions in detail on the specific issues later.

European Communities

94. Chairman, my question then is simple. Do we always have to observe genotoxicity *in vivo* before we conclude that the substance is genotoxic? Thank you.

Chairman

95. Actually, I do have a question. I have a question on what is the meaning of *in vivo* studies and *in vitro* studies. May I ask the experts to respond to this question first before they respond to the question put forward by the EC. Dr. Boobis.

Dr. Boobis

96. Well, *in vitro* means outside of the body, usually in a cell-based system in a test tube or culture dish. *In vivo* means in the whole organism, the intact organism. And because of the many protective mechanisms, both metabolic and repair mechanisms, there is an accepted wisdom that the observation of a response *in vitro* in an isolated cell does not necessarily translate into a response in the whole animal. This is one of the reasons, as far as I am aware, that almost all test strategies for genotoxicity have in them a component that if one is performing a risk-based approach, one would seek to confirm a positive *in vitro* result with an OECD-accepted method *in vivo*, of which there are several.

Chairman

97. Could you respond to the question by the EC?

Dr. Boobis

98. It is pretty well embedded in that response, Mr. Chairman, that the potential is that there are indications of a positive *in vitro*, but that it is not actually described as an *in vivo* genotoxicant or a true genotoxicant with relevance to the risk of that compound until an appropriate study is conducted on mechanisms and an *in vivo* test to confirm that *in vitro* observation. There are examples of compounds which are clearly genotoxic *in vitro* where they are negative *in vivo*, and the risk assessment has proceeded on the basis that the genotoxicity is not expressed in the *in vivo* situation for one of a number of reasons.

Chairman

99. Thank you. You wish to ask a question?

United States

100. Thank you Mr. Chairman. Dr. Boobis, to follow up on your response, if I may. Could you please explain the relationship, if any, between genotoxicity and carcinogenicity? For example, if a compound is genotoxic, is it also carcinogenic?

Dr. Boobis

101. This is the reason I tried to distinguish between, in a narrow sense, genotoxicity and mutagenicity. The answer to the question, is a compound that's genotoxic always carcinogenic is clearly no. There are a number of compounds that cause genotoxicity in *in vitro* tests by mechanisms which are not expressed *in vivo* because of repair mechanisms and detoxification by enzymes of xenobiotic metabolism. What is clearer is that a compound that is a mutagen, a direct-acting, DNA-reactive mutagen, is frequently a carcinogen. But to say that a genotoxin equates to carcinogenicity is not correct and is the reason we place such weight on understanding the mechanisms of genotoxicity and the relevance of observations *in vitro* to the outcome *in vivo*.

Chairman

102. I also would like to remind the other experts that they are free to respond to any questions put forward by the Panel or by the parties. Regarding the parties' questions, I understand that each delegation has its own set of questions to be put forward to the experts on the terms and definitions. So I would appreciate it if you limit your questions at this moment to only those related to answers given by the experts, and then I will give the opportunity for each delegation to put forward its own set of questions to the experts under this particular item. Is this clear? OK. Then as a related question, we understand that experts' responses referred frequently to genotoxic and hormonal mechanisms. What does the term mechanism refer to in this context? And also, as a follow-up question, how a hormonal receptor operates and what hormonal receptor really means. These are two related questions from the Panel. I would give the floor to any of the experts. Dr. Boobis.

Dr. Boobis

103. I propose, if you will, to answer the first half and perhaps one of the other experts can answer the second half. In terms of mechanism, there is this concept that has evolved during the last ten years or more, led by the International Programme on Chemical Safety and others, to try to understand carcinogenicity in a deeper way than simply the observation of abnormalities of growth, which is after all what a tumour is. And this has led to this idea of a mode of action, and a mode of action is a series of key events which are necessary to lead to the formation of the tumour, and these key events comprise the biological changes induced by the chemical and subsequent events which then lead to

the development of cancer. In the case of a mechanism, it is the actual molecular events that are responsible for those changes. So a hormonal mechanism in that sense would mean that it is the endocrine or hormonal effect of the compound that leads subsequently to changes that result in the development of a tumour, whereas a genotoxic mechanism would be where there is a mechanism independent of the hormonal action that results in damage to the DNA directly that leads to the tumour. That is not to say that there aren't situations where both could apply, that there could be elements of more than one mechanism.

Chairman

104. Thank you. Dr. Cogliano, please.

Dr. Cogliano

105. Thank you very much. At the International Agency for Research on Cancer, the expert working groups have been using mechanisms to affect their evaluations of carcinogenicity for approximately 15 years. And the reason it is important to try to understand the mechanism if you can is that sometimes it lets you know that the events, the processes occurring in experimental animals, are relevant to humans, and in other cases it lets you know that the processes that are happening in experimental animals do not operate in humans. IARC has had experience in many cases elevating the concern because what is happening in experimental animals is relevant to humans, and in other cases it downgrades or discounts the evidence in experimental animals because it is not relevant to humans. These principles are spelled out in IARC's guidelines, called the preamble to the IARC monographs. I would also like to say that it is not always necessary to understand the mechanism. For example, many carcinogens, like asbestos, vinyl chloride, benzene were determined from epidemiological studies to cause cancer before anybody had any understanding of the mechanism by which they cause cancer. But when we do have an understanding of the mechanism, it helps us put the experimental evidence in better context about whether it could be predictive of humans or not.

Chairman

106. Thank you. Dr. Boobis.

Dr. Boobis

107. I would just like to add that one of the reasons that such weight is placed on understanding the mechanism and mode of action is that it can inform interpretation of a dose response, and that of course is one of the issues at hand in this dispute. If we understand how the tumour arises, we can also understand what the likely nature of a dose response is.

Chairman

108. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

109. A part of the question was the effects of different mechanisms on carcinogenesis, and we have already talked about the genotoxic effects. That is the direct damage to the DNA. A hormonal mechanism results in enhanced growth or proliferation of certain cells that are responsive to the hormones. You could have an incipient or a single cancer cell that might not grow during the lifetime of the organism, but in the presence of a stimulus such as a hormone, that cell might grow and then become a tumour. So these are basic differences in terminology and that is another reason why mechanism is important, to understand how these different compounds act.

Chairman

110. Thank you. Is any of the experts ready to respond to the second part of my question on what a hormonal receptor is and how it operates in terms of the hormonal mechanism. Dr. Guttenplan, please.

Dr. Guttenplan

111. Yes there are certain cells – my nametag fell down on my controller and I am listening in French and talking in English – alright that sounds better. There are certain cells that have on their surface, if you will, acceptor proteins that can accept oestrogen, and when they accept the oestrogen, they then start to grow, and that's an oestrogen receptor cell, what we call an oestrogen receptor-positive cell. So they would normally grow at a very slow rate or not at all, but in the presence of oestrogen they are stimulated to grow.

Chairman

112. Thank you. Any other follow-up questions? Yes, Dr. Boobis.

Dr. Boobis

113. It is also, I think, relevant that the endocrine system, the system that the hormones act within, is a network of hormones and a network of receptors, and is part of the normal physiological control mechanisms of the body. These hormones evolved as one of the processes whereby we can function as organisms. They are signalling molecules which are transported in the blood from remote sites of production to their sites of action, so they differ from some other signalling molecules which are produced locally. The important thing about a hormone is that it is actually distributed by the blood and is an essential part of normal physiology. So we are looking in terms of hormones as residues against an existing background of hormonal activity, certainly for the endogenous hormones, sorry, the natural hormones.

Chairman

114. Thank you. Dr. Sippell.

Dr. Sippell

115. Yes, I would like to add that this network Dr. Boobis was alluding to is particularly sensitive in children, more sensitive than in adults. And this is very important also in the receptor levels. Some receptor function is really much different from adult individuals in order to allow growth and development at puberty.

Chairman

116. Thank you. Dr. Guttenplan.

Dr. Guttenplan

117. Yes, it is probably obvious to most people, but I just mention a few of the well-known oestrogen receptive organs, which are the breasts, the prostate, the ovaries and the uterus. And a somewhat different comment on genotoxic effects which Dr. Sippell brought to my mind is that genotoxic effects can be a lot more effective if the cell is rapidly dividing, so children represent an

exceptionally sensitive population to genotoxic effects, too, not just hormonal effects on cell replication.

Chairman

118. Thank you. But why is it causing only prostate and breast cancer, other than ...

Dr. Guttenplan

119. Well, nobody is saying it only causes those, oestrogen is probably involved in ovarian cancer and uteran cancer.

Chairman

120. The next question is: what is marker residue? How is it established? And what is a bound residue? Why is it significant? Dr. De Brabander please

Dr. De Brabander

121. Would you repeat again the question, Mr. Chairman.

Chairman

122. What is a marker residue, how is established, what is a bound residue and why is it significant in this?

Dr. De Brabander

123. When a drug is given, or if a compound is given to a human being or to an animal, it is metabolized, and that metabolization is different according to the compound, also according to the species. When it is metabolized, it can be different for humans, it can be different for animals, it can be different in different animals, and if you want, and I go from the point of control, if you want to control that a given compound is administered, you have to look at the metabolite which you will find in a given matrix. What I call a matrix is urine, faeces, meat, whatever is available and you can measure. The marker residue is the residue which you will find. That is a general definition for me as control, it will be different if you look from a veterinary direction. And what is a bound residue? It can be a residue which is bound for example to tissues or to other compounds, so that you must use special techniques to extract it. Thank you.

Chairman

124. Before I give the floor to my colleagues, I will give the floor to Dr. Wennberg and Dr. Boisseau.

Dr. Wennberg

125. Thank you, Mr. Chairman. JECFA has also provided a definition for marker residue, which is in line with what Professor De Brabander has stated. It is a way to actually define what you want to analyse. It is the parent drug, or any of its metabolites, or a combination of these with a relation to the concentration of the total residues of the veterinary drugs in each of the tissues, i.e. the target tissues. What you want to measure is the level of the drug at any time between administration of the drug and the depletion of the residues to the safe level. So it means that to be able to recommend maximum residue limits which will be useful in the control of the safe use of the veterinary drug, you have to

have a method, an analytical method, which measures a chemical substance which relates to the veterinary drug that has been administered, either the drug itself, or a combination of the drug and metabolite, or a metabolite of the drug which is formed in the body of the animal. The definitions of bound residues are the residues which cannot be extracted by the method used to measure the residues of the drug in the tissue in question. There can be different ways of binding of chemical substances to various components of tissue, protein, fats, carbohydrates, etc., and the way to determine whether these residues should or should not be included in the residue definition is a matter to be determined on a case-by-case basis, depending on the behaviour of these bound residues, whether they can be released by enzymatic or other mechanisms, or whether they are actually completely bound and inactivated as such by their bondage to molecules in the tissue. Thank you.

Chairman

126. Thank you. Dr. Boisseau.

Dr. Boisseau

127. Thank you, Mr. Chairman. To begin with, a few words about marker residues. It is a challenge for those who perform evaluations to reconcile the frequent complexity of the metabolization of a substance, which can give rise to a multitude of derivatives of varying concentrations, and with the need for a simple control method. In other words, you have to be able to combine the two.

128. The purpose of toxicological evaluation is to identify, in terms of a toxicological effect that is deemed relevant for the evaluation of the products, all of the residues including the parent substance and the metabolites associated with this toxic aspect. Most of the time, metabolism does not yield one single residue associated with the toxic effect. Thus, to keep the control simple, it is necessary to identify among the residues the one that can be considered a marker residue – in other words the residue that reflects, according to the time in a given matrix, the evolution of all of the residues of concern. Thus, there must be a constant quantitative relationship over time between the marker residue content in a given tissue and total residues of concern – i.e. that are of interest in terms of the toxic effect in question – taken as a whole. As it is not usually possible, however the modern methods used, to analyse different substances at the same time, it is much easier to follow a single residue, the marker residue, which must reflect, over time, the concentration in a given tissue of all of the residues of concern in terms of toxic effect.

129. Now, as regards bound residues, these are what we call – and I do not wish to repeat what Doctor Wennberg has just said – residues that are covalently bound with macromolecules, and in that sense, are not bioavailable – i.e. they are not spontaneously available – as opposed to the so-called free residues, which are not bound to macromolecules. Since for the most part, these residues cannot be extracted, they are identifiable and quantifiable by so-called radioactive methods. Once the content of bound residues in a given tissue has been identified, we have to know what they signify, since the normal metabolism of a substance could lead to the complete degradation of that substance and the reincorporation of very simple monocarbonic elements, for example in the normal protein anabolism in particular. And where you have CO^2, for example, which is radioactive if it is the carbon of the CO^2 that is marked – it is not because this CO^2 is reincorporated in a protein synthesis that it will necessarily pose a safety problem for the consumer. In other words, the mere identification of a certain bound residue content does not necessarily mean that these bound residues pose a problem. Thus, it is up to those conducting the toxicological evaluations – and this is not easy – to go further in the identification of theses bound residues, of their possible release according to the methods that Doctor Wennberg has just mentioned, to see if these covalent bindings could have an impact on the biology of the cell in which they have taken place. Thank you Mr. Chairman.

Chairman

130. Thank you. I now give the floor to Madam Orozco – it is OK? Dr. Wennberg, would you like to take the floor? If that is not the case, Dr. Guttenplan.

Dr. Guttenplan

131. I would suggest for bound, at least the way it is being discussed now, that there should really be a descriptive term there, covalently bound, because bound can be somewhat ambiguous. It just means that it is contained very strongly in a tissue, whereas covalently bound basically means that it is unavailable.

Chairman

132. We have already heard some comments on bioavailability, but I would like you to further elaborate on what bioavailability is, and why is it relevant. Dr. Boobis.

Dr. Boobis

133. Bioavailability is the availability to the interior; the systemic circulation of a compound, in this case via the oral route of exposure, and it can be less than complete because the material is not physically available, for example it is bound covalently to the food matrix, because it does not cross the intestinal wall easily, so absorption is incomplete, or it is metabolized either in the small intestine, the site of absorption, or the liver; because the peculiarity of the anatomy of the digestive system is that almost everything that is absorbed across the small intestine into the circulation first goes through the liver before it gets into the body, and the liver has a tremendous capacity to metabolize compounds. And so for some compounds, drugs and dietary chemicals, it is possible for the small intestine and/or the liver to metabolize to less active or inactive products some or even all of what is being absorbed. So this means bioavailability is less than 100 per cent, what is available to have a biological effect on the body is less than what was anticipated based on the administered dose or the ingested dose. And so in this assessment one would like to know how similar are humans to the experimental animals for example in terms of bioavailability.

Chairman

134. Thank you. Dr. Sippell, please.

Dr. Sippell

135. Again the special case in children regarding bioavailability, as an example for instance we paediatricians or paediatric endocrinologists know very well that a twentieth of the daily dose of the natural oestradiols being used in adult women is already effective in prepubertal girls in stimulating growth, weight development and inducing puberty. So bioavailability is certainly in children much higher in many instances than in adult individuals, and the problem is that pure bioavailability studies which tell us which compound is being absorbed to which extent in a two-year-old or three-year-old or four-year-old child are simply not available because they are unethical to perform in healthy children.

Chairman

136. Thank you. Dr. Guttenplan.

Dr. Guttenplan

137. Another way of expressing bioavailability is to compare the blood dose that one would obtain by injecting the compound intravenously compared to what one actually obtains when one ingests the compound orally. So if you get a much lower effect orally than you would intravenously, you have much less bioavailable compounds.

Chairman

138. You wish to ask a question?

United States

139. Just a clarification, Mr. Chairman. Dr. Sippell, you mentioned, referenced a daily dose in women, can you clarify what dose you are talking about or what sort of treatment of women you were referring to?

Dr. Sippell

140. Daily replacement dose in women who for instance lack ovarian function.

United States

141. And what would the quantification of that dose be? Is there an estimate of the level of that dose in terms of quantity?

Dr. Sippell

142. I mean that's the amount necessary to replace endogenous oestradiol production which is not functioning or absent.

Chairman

143. Thank you.

European Communities

144. Chairman, clarification, what has been said previously by Dr. Boobis on this? Is it always necessary that – either through injection or oral absorption, in order to determine bioavailability – that the drug goes first through the clearing system, the liver, or is there another route which does not necessarily go through the liver? Is this also possible? And do you know if any of these substances enter the human body in that way?

Chairman

145. Dr. Boobis.

Dr. Boobis

146. There are other routes of course for absorption; a small amount will bypass the portal blood supply, which is the one that goes to the liver. It is possible that something could be absorbed into lymphatics. It very much depends upon the physicochemical properties of the agent that is being absorbed. Of course early on oestrogens were trialled in adult patients for therapeutic purposes and it

was apparent then, in those early studies, that there is a very substantial metabolism in the liver which made them unusable for nonhepatic targets in adult males, and this is the reason that they are given by other routes; to bypass that very extensive first-pass metabolism, pre-systemic, pre-absorption phase of metabolism. So there are data in adults. I mean I certainly take the point that has just been made by Dr. Sippell, that these data are not available in children, but in adults there are actually data in human subjects. But I would like to add an additional point about the ethical nature of the question of data gaps. There are studies that one could envisage to answer the question as to whether a child has similar or lower first-pass metabolism without giving a hormone. There could be oestradiol present in normal food; and we have done such studies on other compounds where it would be unethical to give the compound itself. But because it also occurs in low dosage as part of the natural diet it is possible with sophisticated analytical chemistry to design a natural experiment, which is that you just look at what is in the diet, measure what is in the blood and then determine whether there is any change. So one can think of experiments, if there is considered to be a data gap, to seek to address that data gap.

Chairman

147. Thank you. Now the floor is for Madam Orozco.

Ms Orozco

148. Yes, thank you. I had a question for Dr. Sippell, because I assume that something similar happens when you want to test or give drugs, medicines to children. You have to know what is the bioavailability, so how do you find out the bioavailability of other substances?

Dr. Sippell

149. That is indeed a very difficult question and there are special regulations to protect the integrity of children. You know, if they are not healthy, then you can do – with the informed consent of parents and guardians – you can do such studies, but you cannot take blood, for instance, just to study bioavailability. This is unethical.

Ms Orozco

150. Just one question. How do you find out what is the bioavailability of medicines that are being developed for children?

Dr. Sippell

151. Yes, that is a very very difficult question, and I am not a paediatric pharmacologist, but this is very much debated, how this can really be done. It cannot be properly studied as in experimental animals or in adult people.

Ms Orozco

152. Do you know how it has been done until now? Because if one goes to any pharmacy one will find a cough syrup for children, and someone has studied how much is its bioavailability in the child, because we know that one spoon or two spoons would be enough or too much.

Dr. Sippell

153. Most medications we prescribe or give to sick children are not licensed for, let's say, infants or young children, because there have never been done proper studies, as in adults. It is just by experience, by empiric, and that's a big big gap in our knowledge, that we for instance cannot do

metabolic studies in infants or in small children. You know the access to their circulation is so difficult, and if some of you have ever done a blood puncture in a premature infant or so, its really very very difficult, and I am not aware of any big trials which can, or have been applied, to study these bioavailability factors.

Ms Orozco

154. Just one last question. Nowadays a child, maybe two years old, might fall ill, might have an infection, might have a virus, and antibiotics are being suggested. So somehow until now someone has been able to find alternatives to find out more or less what bioavailability is, or at least to be able to estimate it drawn from something else. Do you know how?

Dr. Sippell

155. Exactly. We deduce from adults or from young adults, and of course observe any risks that are being observed, you know the reactions and so on, and in general this is of course explained to the parents and it's compassionate use, it's, as we call it, individual trial in a sick child. That's easy.

Ms Orozco

156. I am not asking about extreme cases, because there are situations where there is need to consent, but for example something which is daily occurrence, you go and you buy a syrup for coughing, or – it should not be, maybe, but it happens all the time – that antibiotics have been prescribed as a medicine, they are prescribed to a lot of children since a very early age, so it is common occurrence what I am talking about.

Dr. Sippell

157. This you can study of course with their metabolism, their absorbance and their bioavailability in sick children. You know that when a new antibiotic comes up, then of course we are doing studies in our patients. That is different from the healthy population in children. Do you understand what I mean?

Ms Orozco

158. Not really, because when a person, an adult, takes a child to a paediatrician because it's ill, the paediatrician will examine the child and conclude you need this or that. You go out from there, you go to a pharmacy, no one asks you anything; if it's known that that medicine at that dose is ok, there is no further clearance, so somehow the system has been able to identify ways to make sure to every consumer that it does not pose a problem. What I am trying to find out is: in the normal cases until now, how has society been able to estimate the absorption in a child?

Dr. Sippell

159. Just by guessing. Even the dosing is in many many instances pure empiric. In modern drugs its somewhat better, but in the past these old standard drugs have never been tested properly in clinical trials and therefore many of these drugs in Europe have lost their licence and have to be retested and this creates tremendous ethical problems. And that is a problem of paediatric pharmacology worldwide.

Chairman

160. I give the floor to Dr. Boobis first and then to the United States.

Dr. Boobis

161. Just in the interest of clarification, Chairman, I would like to make a couple of points. One is that it is important, when we are talking about children, we don't lump them all together, it is critical to recognize that an infant is not the same as a prepubertal child. There is a tremendous range of biology and physiology that changes from early childhood onwards to adulthood, and we have to treat them as distinct groups, and the effects of the hormones will vary as well depending upon the age. We don't use this term child to encompass everything under puberty.

162. And the second point is, it is actually possible for some compounds to design experiments that do not require you to take invasive measures. It is not necessary to take blood always to get some measure of what is in the circulation. Two examples would be a saliva sample, which could be acquired just by passive and non-invasive collection, and similarly the collection of excretions, particularly urine, where, if the compound is largely excreted as a parent or metabolite in the urine, one can get comparative information on bioavailability. So it is not always necessary to use invasive blood sampling techniques to get some indication of whether the compound is absorbed and the nature that the compound is absorbed in. It is just for clarification, if one is thinking about data gaps that might be filled in the future, for example. There are possible strategies that exist to do that.

Chairman

163. Thank you. The US.

United States

164. Thank you, Mr. Chairman. I think that Dr. Boobis just spoke to the point I wanted to raise. Thanks.

Chairman

165. Thank you. EC.

European Communities

166. Could we ask the representatives of the international organizations, in particular JECFA, whether this type of experiments for the residues of these substances which we are talking about here in children or in adults have been performed so that we know what one member of the Panel, Madam Orozco, was looking for, whether this has been done in this case, and why not. For example, when the United States has licensed these substances, why did it not look and why did it not perform these kind of experiments here for example. Thank you.

Chairman

167. Is the representative of JECFA ready to respond? You have the floor.

Dr. Tritscher

168. I don't think we are in a position here to give the detailed response as to exactly what type of data were submitted and looked at by JECFA in individual compounds, that is not our role here. And I would like to point out that JECFA is not a regulatory authority, so we are not talking about drug registration; it is not a registration authority, which is very different. Studies as were just referred to would have to be partially done and submitted to a regulatory authority that registers drugs for specific drug uses. JECFA looks at scientific data, toxicological data and human data, epidemiologic

or experimental studies of any kind that are submitted to the experts or that are publicly available in the published literature. And I am in no position now – I would have to go back to all the individual evaluations that have been done and that have been published in order to find out if any specific studies in children or young infants would have been performed. I am not aware of this.

Chairman

169. EC.

European Communities

170. Well, Madam, we are aware of what happened and we can tell you now; because, as you know, when JECFA evaluated these substances in 1988, all of the five substances, and in 1999 the three natural hormones and in 2000 for melengestrol acetate, we know from what we have seen that none of these experiments involved the kinds of experiments Madam Orozco was asking about. So we would appreciate if the member of JECFA goes back next week or the week after and has a look and can inform the Panel where this indeed has happened. We will give you the time to do that if necessary. Thank you.

Chairman

171. Thank you. Dr. Tritscher please.

Dr. Tritscher

172. With all due respect I am not sure what this really would contribute to go back on all these individual things if you already say that you also have an answer to that. The question is a different one to me: what is the relevance of this kind of study in light of the overall weight of evidence, in the light of the overall data that has been submitted and that has been looked at?

Chairman

173. May I remind delegations again we are now on the first area, on terms and definitions, so I would like you not to go into discussions on the other specific issues. EC.

European Communities

174. Chairman, this is all fine and we can let you go on asking questions, no problem, but please bear in mind that we will have other questions later on, and it is only for that purpose we intervene. We restrain ourselves from intervening really in order to give you the time which you think you need to clarify these questions, but we will have questions to ask on practically the same issues which are being discussed now. So with this understanding there is no problem from us of not asking questions now.

Chairman

175. Thank you. It is quite clear to the Panel. Dr. Boobis you would like to – thank you. And the next question from the Panel is very technical and I don't even know whether I can pronounce the terminology correctly but I will try. Please explain the units used in measuring hormone levels, for example in Dr. Boisseau's response to question 38 of the Panel, in particular please explain ng per ml is or pg per ml, ng per person per day, microgram per day, and how they are converted. Dr. Boobis.

Dr. Boobis

176. There are two main ways of expressing units – actually, I was going to introduce another unit which is micromoles, but I will stick to two at the moment. These are masses per unit volume, so the base would be grams per litre, where we have so much mass in grams per one litre of liquid. They are scaled to units of 10 according to the Système international, the SI units, so they go: micro is 10 to the minus 6 of a gram, nano is 10 to the minus 9, pico is 10 to the minus 12. In expressing dosages in an animal study or with respect to human exposure we often divide by the body weight, so we get so many nanograms per kilogram of body weight per day. So that is where the kilogram comes from, that is to normalize it to the weight, and that is because many effects scale from one species to another – although how much is open to discussion, but that is a scientific debate – on the basis of body weight. So, in other words, if we give a microgram to a mouse it is not equivalent to giving a microgram to a human, because a mouse is so small, so we divide by the body weight to get a body weight-normalized dose, which allows a better – not ideal, but better – comparison of dosage. I was going to introduce the micromole if you wish me to clarify that, which is based on molecular weight, so it essentially allows compounds to be compared on the basis of how many molecules of one to how many molecules of another. Because when you take a small molecule, one gram is going to represent more molecules than when you take a large molecule; and if it is interacting with a receptor it is the number of individual molecules that counts, not the absolute weight, so sometimes we express them in terms of moles. I agree it is a technical issue, discussion.

Ms Orozco

177. Just one clarification. This, for example, nanograms per millilitre – is it already normalized by body weight or is that a second stage?

Dr. Boobis

178. A separate stage. This is a concentration, nanograms per ml.

Chairman

179. Thank you. Dr. De Brabander please.

Dr. De Brabander

180. Thank you, Mr. Chairman. I used to teach analytical chemistry and residue analysis to veterinarians, so I developed something to help them understand these units and maybe it will help also the Panel, so it is just not technical. If you start from a lump of sugar which is approximately 6 grams and you put that lump of sugar in a can of coffee, which is approximately 0.6 litres, you have approximately 1 per cent. When you put it in a bucket of water, then you have 1 per cent, and we are familiar with that because in alcohol control we are in that unit, 0.5 per cent is the limit in Belgium. When you go down and you place the same lump of sugar in a truck which is bringing the gasoline to your home, you are in a range of what we say 1 ppm, one part per million, or 1 milligram per kilogram, or 1 microgram per gram. If you go down and you have it in an oil tanker then you are at a level of 1 ppb, or one nanogram per gram, that is to say one nanogram per millilitre. So if you go still down (you can go down and down further) then you go really to very very low concentrations, like if you can imagine that you have a soccer field and you have submerged it with water from 1 metre high, and you take 1,000 soccer fields and you put one lump of sugar in it then you are again a concentration factor of 1,000 times lower. Maybe that can help the Panel understand. It is not very technical, I know, but I try to make it comfortable for you.

Chairman

181. I agree with your point of view on layman's terms explanations, because it was much helpful for us to understand. Dr. Cogliano.

Dr. Cogliano

182. Thank you very much. I would like to address a little bit of the point about the difference between nanograms per millilitre and nanograms per person per day, because at IARC many times we look at all of the studies that are published in the scientific literature, and different investigators will report the doses in different ways, and we need to try to get some kind of common conversion. It helps us to understand, for example, why one study might be positive and another study might be negative. The positive study might have been conducted at 10 times higher dose, but the units are expressed differently. The third one there, the nanogram per person per day, gives a good example of why you do want to perhaps normalize the dose, because a nanogram in an adult woman is very different than a nanogram in an infant per day. You could perhaps normalize it by body weight, but there might be other ways of doing it. The first unit that you have on the board, nanograms per millilitre, is a different way of normalizing it. It is the concentration in the blood, so it is one nanogram per millilitre of blood, and maybe that is an equivalent concentration, maybe it's not.

183. This actually suggests also why mechanism is important. I think you heard earlier this morning from one of the experts that the rates at which cells are dividing is very important, if you have one nanogram per millilitre while cells are dividing very rapidly, that might have different effects than one nanogram per millilitre in an organ where the cells are not dividing very rapidly. So it is important to try to understand the mechanism, and which of these different units of concentration or dose or exposure is most relevant. Now frequently we don't know which is exactly the right one, and we make our best professional judgement on that. But I think – just to help everybody understand – the units that you have up there are really measurements of very different kinds, and it might take a mathematical model or a conversion formula to go from one to the other. But if we do know how to make those conversions, it can help us understand how a dose in different studies or in different populations might relate to each other.

Chairman

184. Thank you. Dr. Guttenplan.

Dr. Guttenplan

185. Just another way of maybe expressing what has been expressed before, a microgram per ml is one part per million, a nanogram per ml is one part per billion, and then if somebody consumes a ml of a compound that was one microgram per ml that person would consume one microgram of that compound for every ml. It may sound simplistic, but it might help people to understand some of these units.

Chairman

186. Thank you. Dr. Boobis.

Dr. Boobis

187. So just two additional points of clarification. Dr. Cogliano has already referred to the concentrations in blood, and the question was raised from the Panel earlier about normalization, they would not be normalized for body weight because – depending on the sensitivity of the receptor – it is

the circulating concentration that determines response, and so one microgram per ml in a human and one microgram per ml in a rat are essentially equivalent. They may not give the same response, depending on the receptor, but they are equivalent because they are distributed throughout the body. And the other point is that, on the nanogram versus picogram, just a simple point of explanation is that the reason we use these different terms, and it does cause a lot of confusion I recognize, is to avoid the situation of getting into a lot of zeros, so if one expressed something that in picograms was 0.00001, we would just convert it back down to the next appropriate unit, to make it a slightly more manageable number, and that happens in both directions, so it is a practical consideration there.

Chairman

188. Thank you. Dr. De Brabander.

Dr. De Brabander

189. Yes, for the benefit of the Panel I should also say that if you work with students, you learn that they have difficulties to work with those concentrations, they really need a training on that. You can put very difficult questions, and what may be interesting also for you is that you should not underestimate the psychological factor, which is coming with how you will say how the concentration is. For example, if you say it is "0.1 milligram per kilogram" it sounds less than if you said "100 micrograms per kilogram" – but both are the same. The psychological factor of expressing the concentration is very important and veterinary students should learn to see through that.

Chairman

190. If there are no other follow-up questions, then the Panel's last question on this item is: what are xenobiotics? Dr. Boobis.

Dr. Boobis

191. They are from the Greek root xeno, foreign; biotic, to the life, so they are compounds that are not produced naturally in the body, so they are a whole range of so-called foreign compounds. Usually we exclude from xenobiotics nutrients in the diet, so the essential nutrients in the diet like protein, carbohydrates etc. will not be classified as xenobiotics, but everything else, all the chemicals we are exposed to would be regarded as xenobiotics. It is simply a convenient way of lumping together an awful lot of different molecules.

Chairman

192. Dr. De Brabander.

Dr. De Brabander

193. I agree totally, but I would add to that, if you go through all animals and all human beings the definition of xenobiotic is a little bit different, because some components may occur naturally in some animals and not in other animals and not in human beings. We don't have to go into detail, but it can be confusing if you speak about xenobiotic, it can be xenobiotic in one species and not in another one, and also in certain conditions.

Chairman

194. Thank you for your clarification. This concludes the list of the Panel's questions on area 1, and I now give the floor to the parties to ask their own questions to the experts under this particular item. The floor is open. I will give the floor to the EC delegation first.

European Communities

195. Thank you, Chairman. So in this broad area of terms and definitions we have one question first addressed to experts, in particular Dr. Boobis and probably Dr. Guttenplan. Dr. Boobis says in his reply to question number 2, where the definition of steroidal oestrogens is provided, at the end of his reply, that these substances – steroidal oestrogens – act through oestrogen receptors, and my question is: is it really the only way they act, is it only through oestrogen receptors, or do they act through another mechanism, one or more?

Chairman

196. Thank you. Is Dr. Boobis or Dr. Guttenplan ready to respond? Dr. Guttenplan.

Dr. Guttenplan

197. The evidence that oestrogens act through a non-receptor mechanism is not strong. There have been a lot of studies of what we call *in vitro,* in test tube studies, but there is some recent evidence that has not been published yet which pretty much confirms that oestrogens can act by a genotoxic mechanism in humans. However, the level is very very low and you need supersensitive instruments to detect it.

Chairman

198. Dr. Boobis.

Dr. Boobis

199. I think it is important that we recognize that there is a difference between what a given oestrogenic compound can do and what we mean by oestrogenicity. So we can argue or discuss whether oestradiol has various properties, but some of those properties may be additional to its oestrogenic activities. Oestrogenicity is a defined biological term and it functions through specific biological pathways, which is not to say that some compounds which are oestrogenic cannot have other properties. So I think we need to make a distinction, we cannot lump everything that is oestrogenic into one chemical class and say that it always has other properties. It is absolutely clear that not all oestrogens have any genotoxicity, not all of them, some of them do, some of them don't. It is probably not a function of oestrogenicity that causes that effect, it is some other property that they have, in the case of oestradiol, it produces quinones; not all oestrogens can produce those structures.

European Communities

200. Gentlemen, I recall, if I may say so, in a statement by Dr. Guttenplan, that these steroidal products, oestrogens, do not act only through the receptor, may they act through another means? And this is my question. Because in his reply Dr. Boobis only says they act through receptors, oestrogen receptors, which is in fact not true. There may be another way in which they act.

Chairman

201. Dr. Boobis.

Dr. Boobis

202. There are examples of oestrogenic antagonists, that were designed to interact with oestrogen receptors for therapeutic purposes, and these compounds have been studied using the most sensitive methods known to man for interaction with DNA, accelerator mass spectrometry, and have been shown to be negative. Now what that shows to me is that the oestrogenic structure *per se* itself does not necessarily lead to the capacity for genotoxicity. I am not saying that some of these compounds might not do that, but I think it would be inappropriate to regard that as a property of their oestrogenicity. That is the point I am making.

Chairman

203. Thank you. Dr. Cogliano.

Dr. Cogliano

204. I would like to say that last year the IARC monographs evaluated combined oral contraceptives and hormone therapy that combined oestrogen and a progestogen at the same time. And the expert working group concluded that both of these kinds of exposures clearly did have receptor activities, but that there was also some evidence of genotoxicity and that it was possible that they acted both through a hormone receptor mechanism and a genotoxic mechanism. The evidence was that it is obvious that they do have a hormonal effect, but the expert working group at IARC last year did conclude that these oestrogens and progestogens that are used in birth-control pills and in hormone therapy could have some evidence of genotoxicity as well.

Chairman

205. Dr. Guttenplan.

Dr. Guttenplan

206. Just to elaborate on what Dr. Boobis said. The oestrogenicity has no direct relevance to the genotoxicity of the compound – different effects. And I think of all the compounds and hormones that are possibly present in beef, the only one that might have genotoxic effects is oestradiol, and these would be very weak but they might still be there.

Chairman

207. Thank you. Does the EC have more questions? EC.

European Communities

208. I would like to ask the experts if they could restate or provide again their views on the mutagenicity in this case and how that relates to genotoxicity, in particular the DNA damage? And what is the role in that respect, and the conclusions we can draw, if a product is or is not mutagenic for the purposes of genotoxicity? Thank you.

Chairman

209. Thank you. Dr. Guttenplan.

Dr. Guttenplan

210. A mutagenic substance alters the structure of the DNA permanently and heritably. So DNA has if you would, an alphabet. If even one letter of that alphabet is changed, you have a permanent heritable change in that DNA, which will be transmitted to future cellular generations. Very few mutations actually are deleterious, most mutations are innocuous. And then of those that have deleterious effects, very few of them are in growth control genes. So the probability of a substance that causes mutations also causing, say, a cancer-causing effect would be very small. An agent that damages DNA is a potential mutagen. That damage is mainly going to be repaired, but if a little bit does not get repaired or is misrepaired – there are DNA damage responses that make errors when they repair – then you can get a mutation. So a substance that damages DNA may give rise to mutations and it may be carcinogenic. As was elaborated before by Dr. Boobis, there are many mechanisms by which chemicals can cause cancer, genotoxicity is only one of them.

Chairman

211. Does that conclude the list of questions from the EC? I give the floor to the US. You have the floor.

United States

212. Thank you, Mr. Chairman. The United States has only one question, so I will keep this brief. I would ask Doctors Boobis, Boisseau and Guttenplan, who I think spoke on the terms and definitions section on similar issues, if you could please explain the difference between oestrogen and oestradiol 17-beta (17β).

Chairman

213. Dr. Boobis

Dr. Boobis

214. Oestradiol-17β is a specific compound. Amongst its properties it can bind to oestrogen receptors. Oestrogen is any compound with a steroidal structure that can bind to those receptors, so it is a class of compounds.

Chairman

215. Thank you. If that is all from the US, then I give the floor to ... Are there any experts to add to the comments made by Dr. Boobis on this question before I give the floor to Canada? If there are none then I will give the floor to the delegation of Canada.

Canada

216. Mr. Chairman, we have no questions at this time on the definitions. The discussions on the definitions has been very fruitful and clarified some of our questions. Thank you.

Chairman

217. Thank you. We have 30 minutes to go before lunch break, but given the time constraints I would like to move on to the next item, that is risk assessment techniques. As was the case for the first item on terms and definitions, the Panel will pose some questions first and then invite the parties to pose their own question to the experts. The Panel's first question is composed of three parts; one is: how are ADIs and MRLs determined? and how do JECFA and Codex interact? The floor is open to answers by the experts.

Dr. Tritscher

218. Thank you. I would like to start with the first part, on how ADIs are set, and the latter part I give over to my colleague. In this context I would like to refer to the basic document that explains how ADIs are set. I will make it very brief in my explanation, but it is explained in detail in Environmental Health Criteria 70, Principles for the Safety Assessment of Food Additives and Contaminants in Food, published by the World Health Organization in Geneva 1987. Again in the interest of time I will make it very brief and basic and then if there are additional questions I think I can explain later. ADI is an acceptable daily intake and is a chronic health-based guidance value. It denominates the amount that can be consumed over lifetime without appreciable health risk. As Dr. Boobis alluded to in the beginning, appreciable is not a legal term or anything like that in this sense, it just denominates the basic concept in toxicology that there is no zero risk, there is always some level of risk.

219. Now the accepted daily intake is established from the overall toxicological database. Experts review all available data, and since it's a chronic long-term guidance value the emphasis is on long-term studies. Mostly we talk about experimental studies from experimental animals that are treated under very defined circumstances and conditions with the specific compounds of interest. And from these studies no effect levels are determined; levels of exposure that do not lead to any adverse health effects in the test species. I have to add that sometimes of course there are also human data available that are also taken into consideration. From this no observed adverse effects level in the experimental studies it is then – with a number of uncertainty factors, or also called safety factors – extrapolated from experimental species, if we talk about animals, to the human situation. With another uncertainty or safety factor it is then taken into account that there is possibly broader variability in the response of the human population as compared to a more defined experimental setting, so that no observed effect level is divided by these combined safety or uncertainty factors in order to arrive at an acceptable daily intake level for the human population. Mr. Chairman, is this sufficient as a brief explanation for the Panel?

Chairman

220. Yes, I suppose so. May I ask Dr. Wennberg?

Dr. Wennberg

221. The acceptable daily intake is established by JECFA. To then go through the procedure which is used by JECFA since JECFA started to evaluate veterinary drugs, is to derive the MRLs from the data on the pharmacokinetics, the metabolism and depletion of the residues from the tissues after the last administration of the veterinary drugs in the animal in which the product is to be used. JECFA has developed a decision tree procedure to arrive at the maximum recommended maximum residue limit, which consists more or less of the following. As we were talking about the marker residue before, JECFA determines what is the most appropriate marker residue in the circumstances for the various tissues which have been chosen by JECFA to be included in a standard food basket to be consumed every day. This food basket consists of 300 grams muscle, which is meat, 100 grams

liver, 50 grams kidney, 50 grams fat, 1½ litres of milk, 100 grams of eggs and 20 grams of honey – in the case of milk and eggs and honey, if the product is to be used in lactating animals, laying hens and honeybees, respectively.

222. Then JECFA requires a study using a radio labelled compound, which means that the substance, the veterinary drug, is marked so that all the molecules of the substance can be found in an animal and compared to the amount of the marker residue which can be found by the analytical methods that I will come to later, which is used to analyse the marker residue. Then the recommendation of the MRL is an iterative process which has been described in our answer to question number 9, in that JECFA tries to find the balance of the values where, given the depletion of the residue from the various tissues, which can be different, as a marker residue can remain longer in the liver or longer in the fat or longer in the kidneys. So for the practical purposes of using veterinary drugs, to establish a time where all the residues, if they were targeted for the specific food basket, would be below the ADI. So to try to balance the different levels of the total residues to the marker residue with the different concentrations at different time points in the tissues of concern, JECFA is making these calculations to make the best fit. And if, for example, the first calculation results in that the sum of all the total residues are significantly above the acceptable daily intake, then of course one has to adjust the calculations to arrive at final recommendations of the maximum residue limits for the marker residue, which if the drug is used according to good practice or use of the veterinary drugs, as defined by Codex, would result in the total residues being below the ADI. And then I could remind maybe the Panel and the rest of the experts and the parties that the food basket that has been chosen by JECFA is quite a substantial amount of food from animal original to be consumed every day. So in a sense it is also an over-estimation of the consumption of residues.

Chairman

223. Thank you. So who is going to respond to the second part? Dr. Miyagishima please.

Dr. Miyagishima

224. Thank you, Mr. Chairman. Let me briefly explain how Codex interacts with JECFA. As I mentioned in my introductory remarks, Codex is a risk-management body and, contrary to the perception which some people have according to which everything starts with risk assessment and then is followed by risk management, in the Codex/JECFA system the story starts with risk management, and the first component of risk management, called preliminary risk management activities. First of all, in the specialised Committee of Codex dealing with residues of veterinary drugs in foods, CCRVDF, the discussion takes place as to what compounds in what foods may pose public-health risks or may lead to barriers in international trade. And the Codex members in this Committee discuss, among themselves, on what compounds new work should be started within the Codex system. Of course they take into account various factors, such as whether the product itself is available as a commercial product, whether good agricultural practice has been established that goes with the use of the compound, whether there are sufficient amounts of scientific work that would warrant sound assessments by JECFA. When these conditions are considered to be met, then the CCRVDF puts the compound on what we call the priority list for evaluation by JECFA, and this is sent to JECFA for evaluation. You can put in this list compounds that were already evaluated by JECFA in the past, or you can put a new compound that has never been evaluated by JECFA; you can nominate a compound for which the Codex has already established an MRL, or you can also include a compound for which no Codex MRL has been established. It is up to the CCRVDF to take various conditions into account and set priority for compound assessment.

225. After JECFA has conducted risk assessment on these compounds, and when the result, including the recommended MRL, is sent to CCRVDF, CCRVDF usually sends or circulates the recommended MRL at step 3 of the Codex step procedure; that is the step at which government

comments are invited. The comments made are considered and are looked at at a physical meeting of CCRVDF at step 4, and then MRLs usually follow the way through the final adoption at step 8; and of course at each step the Codex will have due regard to the scientific output of JECFA, but also take into account other factors that are deemed necessary to be looked at. And in this process there is interaction between Codex and the JECFA system. If Codex, namely CCRVDF, wants to have more information on certain issues, CCRVDF has the ability to ask those questions, either general or specific, to JECFA, and also Codex may request a particular type of risk assessment or scenario analysis and other kinds of supplementary information to JECFA, and it is up to JECFA to answer those questions. Thank you.

Chairman

226. Thank you. I understand that Dr. Boisseau would like to add. Before I give the floor to Dr. Boisseau, may I give the floor first to Dr. Tritscher please.

Dr. Tritscher

227. Thank you very much. Just to emphasize again the ADI and MRL and the interaction between JECFA and Codex. The ADI is established by JECFA; it is the outcome of the risk assessment, if you want, and it is not for discussion at the Codex, so that is a value that is established by the risk assessment body. The MRL as it is proposed by JECFA, is based on scientific studies and data that are made available to the expert body and that are evaluated by the risk assessment body, by JECFA, and then the MRLs are proposed to the respective Codex Committee, CCRVDF in that case. And then the risk management body, so the Codex, the CCRVDF is the risk management body, takes this proposal into account and can consider other factors in setting the final MRL. That is all it is, just to emphasize it again. Thank you.

Chairman

228. Thank you for your clarification. Dr. Boisseau has the floor.

Dr. Boisseau

229. Thank you, Mr. Chairman. I agree, of course, with what was just said by the three preceding speakers. I would simply like to add a few details. We are accustomed to saying that in order to determine an admissible daily intake, we perform an evaluation of the toxicological profile of the substance studied. In fact, toxicology is a somewhat narrow term, since the experts will focus not only on the toxicological effects, but will be looking for all of the undesirable effects which, in addition to the toxicology, could include physiological and microbiological effects. And for each study concerning one of these aspects – toxicological, physiological or other – the experts establish an intake that has no effect, and depending on the nature of the undesirable effect observed, they will allocate to that intake which has no effect an appropriate safety factor which may range from ten to 1,000, enabling them to obtain a series of acceptable daily intakes. Finally, the committee – the CVMP or the JECFA – will select the most restrictive of these daily intakes, in other words the one that is most protective of public health. So it is important to take account of the great variety of tests involved and the fact that at the end of the day, the daily intake selected is the one which is most protective of public health. You will probably ask later on about the safety factors considered throughout the process of determining the ADI and the MRL, so I will not address that issue now.

230. Let me add that usually, these toxicological studies are experimental studies that are conducted with the parent substance for practical reasons. But where feasible and justified in view of the toxicological profile of a given metabolite, this kind of study can also be conducted with a

metabolite whose toxicological or pharmacological profile could make it the limiting factor in terms of the evaluation of the safety of the residues.

231. Finally, I just wanted to add a word or two, if I may, on the distribution of the risk assessment and risk management tasks between the JECFA and the Codex. It is customary, in conducting a risk assessment of an environmental product, for the scientific committee to conclude its risk assessment with an indication of the probability of risk for a given population or sub-population. The residues of veterinary drugs are a somewhat special case, since we control the administration of veterinary drugs to animals, and the JECFA therefore goes beyond the mere appreciation of the risks, since that appreciation more or less stops with the determination of the ADI. With the determination of the MRLs, the JECFA is deliberately entering into the realm of risk management, since an MRL is a tool, a proposal to ensure that the ADI is not exceeded with regard to the standard food basket as mentioned a short while ago by Dr. Wennberg. This is a somewhat special case, since one can effectively manage the situation and the objective. The objective is not only to assess the risks, but also to minimise the risks to which consumers of foodstuffs of animal origin could be exposed.

232. However, this does not detract from the JECFA's responsibility for risk assessment and the responsibility of the Codex Committee (CCRVDF) for risk management, since when it comes to MRLs, the JECFA, which is a competent scientific committee qualified to make proposals, makes proposals only, while the risk manager – in this specific case the CCRVDF – is the one that takes a decision. In other words, the fact that the JECFA makes MRL proposals on the basis of the competence of its WHO or FAO experts does not mean that it can be accused of interfering in risk management. It is the decision maker that manages the risk, i.e. the CCRVDF with the Codex member states. Thank you.

Chairman

233. Thank you. Dr. Wennberg.

Dr. Wennberg

234. Thank you, Mr. Chairman. Yes, could I just add a few comments, also regarding the possibility of temporary MRLs, or is that another question that you have? So JECFA will make full recommendations for quantitative values for MRLs if there is adequate data to do so and if this is in accordance with the ADI. There may be instances where there is enough information to recommend MRLs, but the analytical method to determine these MRLs has not been sufficiently validated to the use in control laboratories worldwide. In such instances, as the process in Codex is quite long, JECFA may recommend temporary MRLs, and providing an opportunity for submission of additional information to a next meeting or a future meeting of JECFA for evaluation of the validation of the analytical method. This has happened on occasion. Also the Committee of JECFA may recommend MRLs not specified, or unnecessary as it was termed in very old reports, where there is a wide margin of safety of residues when compared to the ADIs, and which would mean that it is not necessary to control this substance when it is used in accordance with good veterinary practice, because the values will never come anywhere close to the ADI. And finally, of course, if there is not enough information for JECFA, and there are deficiencies in the data available to the Committee, they will of course not recommend MRLs and they never have recommended MRLs if there is no ADI established.

Chairman

235. What do you mean by temporary? When and under what conditions will temporary MRLs be terminated?

Dr. Wennberg

236. Temporary MRLs are recommended with a qualification that if the specified information, which is also specified in the report, is not submitted within a certain timeframe, then the MRL will not exist anymore. So if the JECFA Secretariat does not receive the required information, the appropriate following meeting of JECFA will take the decision that a temporary MRL will be revoked. And this information is transmitted to the CCRVDF and Codex.

Chairman

237. Thank you. As it is already ...

Ms Orozco

238. Just one qualification please. What kind of criteria are brought into consideration when an MRL is being considered; information that is different than the one that has been taken into account by JECFA? What kind of other criteria or other information is it taken into account by Codex?

Chairman

239. Dr. Miyagishima.

Dr. Miyagishima

240. Thank you very much. Indeed, within the Codex system there has been a lot of discussion that took place to better delineate those factors that can legitimately be taken into account when Codex elaborates texts. In fact the Codex Alimentarius Commission adopted in 1995 a statement of principle concerning the role of science in the Codex decision-making process and the extent to which other factors are taken into account. There are four paragraphs and these statements are reproduced in the Codex procedural manual. Later, in the year 2001 there were additional criteria adopted by the Commission that assist in the consideration of those other factors referred to in these statements, and this text is also included in the Codex procedural manual. Basically, the factors that may be considered as relevant for the protection of the consumers' health and/or for ensuring fair practices in the food trade can be taken into account and they can be moved by any members of the Codex bodies. It is up to the CCRVDF and ultimately to the Commission to weigh those factors and incorporate and take account of them in making a final decision. One could give some specific examples but I would rather not mention them at this stage. Thank you.

Chairman

241. US.

United States

242. Thank you Mr. Chairman. Just a quick follow-up on the response of the representative from JECFA, just a point of clarification. Did JECFA make full recommendations for MRLs for each of the six hormones involved in this dispute?

Chairman

243. Dr. Wennberg.

Dr. Wennberg

244. Thank you, Mr. Chairman. Well, the six hormones which are the matter of this dispute, as far as I understood, are oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol and melengestrol acetate, is that correct? OK. So JECFA evaluated the three endogenous hormones, the first three ones, and on three occasions; in 1981 only for general considerations; in 1987, concluding that an ADI was unnecessary; and in 1999, establishing ADIs for all these three hormones. At the same time, a complete residue evaluation of these hormones was performed and is available in FAO Food and Nutrition Paper 41/12, and concluding that it was not necessary, on the basis of the residue data, to recommend full MRLs for these three hormones. As regards trenbolone acetate, JECFA evaluated this substance four times; in 1982, general considerations; in 1983, limited by good husbandry practice; and in 1987 and 1989, established first a temporary and then a full ADI. In the same way the residue data were evaluated and no MRLs were considered. No that is not correct. Can I have the lunch break to go back to the data and see about these three other substances, whether there were MRLs established for those?

Chairman

245. Sure. If you don't have the information now then you can do so. I would appreciate if you can respond to all the questions as briefly as possible. It is already 1 o'clock, so now I would like to have a lunch break and resume the discussions at 3 p.m. sharp in this room. I will see you all this afternoon at 3 p.m. Have a good lunch.

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Chairman

246. [Beginning of tape] ... when our discussions were suspended, we were on the issues related to ADIs and MRLs and I believe that issues on this item, the risk assessment techniques, are at the heart of the discussions this afternoon. The Panel has a rather long list of questions, but as we understand it the parties are also very eager to put their own questions to the experts. I would like to be as brief as possible, not only in our answers and questions, but also I would appreciate if the experts will be very brief and succinct in their replies to the questions so that the parties can have more time to ask their own questions later.

247. The two follow-up questions regarding the first one I posed this morning also relate to ADI and MRLs, so I would combine these two questions together. My question is: does the ADI take into account the fact that some of the same hormones exist in other food and medicinal products and that therefore there are other sources of intake of the same compounds? The second one is: does the ADI take into account all uses of the hormones as veterinary drugs, including for example for zootechnical purposes? The floor is open for comments and replies, from JECFA first, and then I will give the floor to Dr. Boobis.

Dr. Tritscher

248. Thank you Mr. Chair. If I may ask, I happen to have slides on my computer that explain this and answer actually the two questions.[2] Just very quick, to the first question about the interactions of JECFA and Codex. This is illustrated here, but we have discussed, so JECFA as a risk assessment body interacts with the Codex as the risk management body. (Can I have the next slide please.) Now this illustrates what we actually do with the ADI and the exposure assessment, and this is to answer questions (b) and (c) that was just raised, if JECFA, in setting the ADI takes account of all possible

[2] Dr. Tritscher's slides are contained in Attachment 2 to this transcript.

exposures, to simplify the two questions. As I mentioned briefly earlier, the ADI, the acceptable daily intake, is the outcome of the toxicological evaluation, and as was mentioned earlier by one of the experts, in the case of veterinary drug residues, its toxicological effects, physiological effects, pharmacological effects, as well as microbiological effects are considered, and from that an ADI is derived.

249. Now the exposure assessment is then done separately from that, so in setting the ADI exposures are not considered. Exposure assessment is done separately in that the amount of the chemicals in the food times the amount of food consumed is considered, this is the exposure. And in the actual safety assurance you compare this estimated human exposure with the ADI, so if the estimated exposure is below the ADI, then the situation is OK, if the estimated exposure is above the ADI, then a risk management decision has to be taken. That can also be, from the risk assessment point of view, in the first step the refinement of the exposure assessment and so forth, so in an iterative process refining the exposure assessment and then comparing it with the ADI. Basically, and sure to answer the question, the exposure assessment is done separate of the ADI, so in a subsequent step the exposure has to be compared to the ADI in order to ensure safety of the overall food supply.

250. Very quickly a few comments on the international field, so from the perspective of JECFA. The exposure assessment in the case of veterinary drug residues, as my colleague from the FAO explained earlier, is based on a food basket diet, so on a model diet. In a national setting, exposure assessments can be done in a more refined way, because more specific data for that country would be available, for example with food consumption patterns and so forth. So in the international field, in the case of veterinary drugs we work with model diets in order to assess the estimated human exposure and to compare it with the ADI. And also, then the estimated exposure is compared with the MRLs that JECFA proposes in order to ensure that they are compatible with the ADI and hence they are compatible with public health. I would leave it at that and would ask you if you have any additional questions.

Chairman

251. Thank you. Dr. Boobis – ...yes, EC.

European Communities

252. To change the subject a bit right now, because all of the things that you have not been told is that there is a lot of data that you can't get because you don't have enough animals to do the testing, in many cases, and so there are assumptions made, what the dose-response curves looks like when there is no data, so it's a guess. These assumptions are a weak scientific statement and there are dozens of these assumptions, and one of them is that there is a threshold, a dose below which there are no adverse effects. A threshold is a theoretical concept and it is difficult or impossible to actually measure, because there really are not enough animals to be able to determine that there is a threshold or not. It would take thousands of animals and you could still find arguments that there are other data that suggest that these assumptions are not right. When there is a hormone that the body is making and is in circulation, and when you add more of the same kind of hormone, such as an oestrogen, you are just increasing the response that is already taking place, and in that case there cannot be a threshold. The threshold has already been exceeded by the concentration of hormones in the circulation. So this specific set of conditions results in dose-response curves that will have no threshold, and if there is no threshold, there is no safe dose, unlike the suggestion that there is an acceptable daily intake, and in a lot of cases an acceptable daily intake is legitimate, as long as there is not a counterpart to the chemical that you are giving and it does not exist naturally in the body, then you have the opportunity to at least justify an acceptable daily intake. But when those hormones are circulating and are already active and you add more hormones, particularly at lower doses, what you expect to get is an increase in the adverse effects, and under these conditions an ADI has no meaning

whatsoever. There will be risk at any dose no matter how low, and both Fred and I have demonstrated that at experimental studies and we have nobody that has been able to tell us or to show us where what we have done experimentally, and what we have done in terms of our conclusion, no one has shown us that it is wrong.

Chairman

253. US.

United States

254. Thank you, Mr. Chairman. Two quick points, one a point of clarification. The United States was under the impression that this was the opportunity of the parties to ask questions of the experts selected by the Panel rather than presenting evidence of perceived situations ourselves in response to Panel questions. On the second hand I would refer back to the Panel's e-mail or letter of last week noting that the evidentiary record in the proceedings had in fact been closed but for a showing of good cause to present new evidence, and we would note that a presentation of evidence as we just heard could fall within the ambit of that letter. Thank you.

Chairman

255. As I mentioned this morning, the purpose of this meeting is to request the experts to assist the Panel in discharging our duties as panellists, so it is quite clear to us. I also mentioned that parties will be given more opportunities to put their own questions at a later time in due course. So I would ask the delegation to limit their questions and comments or replies to those particularly related to questions put forward by the Panel. I give the floor to the delegation of Canada.

Canada

256. Thank you very much, Mr. Chairman. First of all, of course we want the Panel to get as much information they can out of this process and out of the experts as possible, and we certainly are not in any position, we don't want to limit the flow of information to you. But in the same vein as the questions raised by my US colleague, and we support the point, I guess as a matter of clarification, you mentioned questions may be put, I would like to know whether questions also includes arguments and expert testimony by members of the delegation of one of the disputing parties? I think, to the extent that we are talking about questions, that presumes that we are not talking about arguments or running monologues, or we don't want to get into a debate or discussion with the experts at this point, it would seem to me.

Chairman

257. Yes. As I made it clear in the opening statement this morning, the questions and comments have to be focussed on the information and replies given by the experts in written form. So I make it clear once again that the discussions that we are going to have this afternoon will also be focused on the information and comments and replies by the experts, without going further into the arguments on legal issues and those factual issues which have to be discussed next week on Monday and Tuesday. Is that clear to every delegation. OK. With that understanding …

Ms Orozco

258. Thank you, Mr. Chairman. I have a follow-up question to the information that has been presented by JECFA. In the case of hormones, for example, it is clear, as we have been told, that there are hormones in different types of food, so when you take establish the ADI, are you taking into

account the level of hormones that there is from the consumption of every product that contains hormones in an endogenous way?

Chairman

259. Dr. Boobis? JECFA, Dr. Tritscher

Dr. Tritscher

260. Just very quick. In the MRL derivation, the experimental studies are done in the actual food-producing animal, as it's called, so by default you have the levels that are measured in these studies contain endogenous levels of hormones as well, so if you want, by default they are included in this consideration.

Ms Orozco

261. Yes, but what I would like to understand is, it is the addition of all the hormones that you would intake in your diet, because I don't know if it is set by the product, by meat for example in this case, or if it takes into account all the intake of hormones, because you eat different things. That was the first part of the question, and I'll just explain to you the second part of the question, so I don't have to repeat so many times. In the same vein, do you take into account the intake of a veterinary residue that would exist of the same compound because of other reasons, so we have also seen that there are veterinary drugs that use hormones that are used for zootechnical treatments. Is that reflected in any way in the ADI?

Chairman

262. I would appreciate it if the replies would be right to the point, as succinct and as brief as possible, given the time constraint. OK?

Dr. Wennberg

263. OK. Thank you, Mr. Chairman. Well, the questions that are asked to JECFA from the CCRVDF are particular questions on the assessment of a particular residue or a veterinary drug, and it is used according to good veterinary practice. It's also said that for JECFA to assess a veterinary drug, it has to be authorized at least somewhere in the world, so there has to be a national authorization somewhere. I think we have to make it clear once again that JECFA is not a regulatory authority that authorizes the use of drugs. So the questions that are asked to JECFA are related, in this case of the natural endogenous hormones, to their use as production aids in cattle. So what JECFA has evaluated is first of all the toxicological evidence which enables JECFA to set ADIs, which is irrespective of the exposure, as we have just heard. And following on from that JECFA evaluated the concentrations of the hormones, as evidenced by the residue depletions studies and taking into account the endogenous concentrations of hormones in the meat.

264. Now, the endogenous concentrations of hormones in the meat are variable, and so its not possible to say that is X, Y or Z, because depending on the reproductive cycle of the animal, these levels vary. They can be high at certain times and low at certain times for the different hormones. So JECFA evaluated how much of the additional residues relating to the use of the hormones in question would represent in terms of the ADI, and we come to a very low figure, it's less than 2 per cent of the ADI for oestradiol, it's less than 0.03 per cent for progesterone and it's less than 0.2 per cent of the ADI for testosterone. That made the Committee conclude that it was not necessary to specify numerical MRLs and recommend MRLs not specified for these three natural hormones. Now, if you are using hormones, you can either use one hormone or you can use a combination, depending on

what kind of effect you would like to have. These uses are to be authorized by national authorities. JECFA does not enter to efficacy of the use of these hormones.

265. When you are using xenobiotic hormones which are not natural, these are also governed by national authorizations, how much you use and under which circumstances. And in these cases, as I was asked before the lunch break, I was going to come back with MRLs that JECFA had proposed, recommended for these substances. So for these substances, ADIs were set specifically for these substances, so they are not put together with other hormones, because the effects that were evaluated in the toxicological assessment enabled the Committee to set an ADI for these specific substances. So you don't consider all different hormones with different kinds of effects and different types of profiles in the same evaluation. So if you use one hormone, that's the hormone that you are using at this time. There may be combinations but if they are authorized on a national level that's it. So for the three xenobiotic hormones, JECFA set full MRLs, recommended full MRLs for all three of them. This is available publicly and unless the United States want me to actually give you the levels, I will make my intervention shorter by not mentioning them. If you have any further questions I will be happy to answer.

Chairman

266. Thank you. So are any other experts intending to add any more comments? EC.

European Communities

267. Gentlemen, I think there are other more simple and I hope more clear ways to reply to the question. Now this is given in the reply of JECFA to question No. 10; it is already in your files. So you will see that JECFA says that they do not take into account data on the intended or actual use and consumption – the way the substances are going to be used or consumed, they don't take data into account. It is in the file. This is the reply to the question, the second of the questions. How they are going to be used and how they are going to be consumed; they don't take this into account. This is a purely generic toxicological study, without consideration of where they will be used for. A body with good veterinary practice or not, whether they would be misused or not, there would be more implants, in one implant there will be more hormones, one, two, three or not, this is not considered. As the doctor has said, it's only a single substance that is analysed.

268. Now for the first question, again on the reply of JECFA to question number 10, you will see they speak about the so-called basket and whether there are intakes of the substances from other sources, and there you will see the basket consists mainly of steak, meat and muscle, meat and liver, meat and kidney and they have milk, eggs and honey, but of course it does not exhaust all the other possible sources which humans eat every day and from which intake of these hormones can come. This is the reply to the first question and it is explained also in the text. Thank you.

Ms Orozco

269. Excuse me, an interruption just for completeness. What other sources are you thinking about? You say that there other ways in the diet of humans, other than the food basket of JECFA, what other sources do you have?

European Communities

270. For example, speaking about butter, I can think of a list of substances a human eats every day. Some of them may contain more hormones, less hormones. Or other kind of meat. So these are things which – I understand it is difficult to devise a basket that is really representative, and the representative of JECFA has said they leave it to the national authorities to see, in each EC member

State, in each country, according to the nutrition habits probably. If one country eats some substances a little more than what is in the basket, they would have to be reviewed, these calculations. But certainly humans one day eat not only 300 grams muscle, 100 grams of liver or 100 grams of kidney and so on. So there are certainly other sources from which we take in these substances. This is not disputed in the science. And if you allow me to clarify, in reply to what has been said by the representative of JECFA – this is very important – the toxicological analysis takes into account a substance individually. We will come back later to this. None of the implants as far as we know consist of one substance only, there is more than one substance. It means the majority of the implants contain more than one of these hormones together, and the data which they have examined, they don't take this into account. The toxicological data they take into account, they don't examine the possible additive or synergistic effects of these implants, and these possible effects they have not been examined because it is not done. It has not been done before by the countries that have authorized these substances, for example. Thank you.

Chairman

271. Dr. Tritscher would like to add some more comments.

Dr. Tritscher

272. Yes, I have to respond to that and clarify a couple of points that were not exactly correct in the intervention by the EC. (May I kindly ask you to put up a second slide, what I have on JECFA MRL, that is what it is called.) This is just a little graph, an illustration how JECFA does residue evaluations. Just to illustrate that it is based on specific detailed studies in the food producing animal. (Thank you, that's it.) As I said earlier, so you have detailed studies in respective animal species for what the veterinary drug is intended to be used for. So by default, and that is what I tried to say earlier, you consider endogenously occurring hormones as well as the additional treatment, that is by default, because that is what you measure in the end if you measure a synthetic hormone for example. So based on these studies, the residues, the MRL, is derived. And then from the studies, from the median residue level in these defined studies according to good veterinary practice – this is very important because it is incorrect what was said before, that this is not considered, it is considered. Only studies that are field trials and studies that are performed under good veterinary practice. And we have a small definition, but the problem here is that there is no internationally agreed definition. But from these studies the median residue level is taken for the intake assessment according to the model food basket, as was correctly said.

273. Now this model food basket was constructed in a way to reflect exactly these commodities as animal-derived foods that may contain veterinary drug residues, and butter, for example, it is self-understanding that butter is covered by milk, because butter is milk fat. So there are all these different types of commodities that are covered in the model basket, in a way, to give you conservative – and conservative in our language means a high level – estimate, rather than going too low. And as I mentioned earlier, or what I tried to explain, is that JECFA has to consider a worldwide model, and I did by no means say that JECFA leaves it up to national authorities to do an exposure assessment. JECFA does do an exposure assessment based on this model diet, taking conservative assumptions to give them an idea of what the estimated exposure on the higher level could be. National authorities have the possibilities, based on refined data, to refine these intake assessments – to use data, additional data, that are adapted to, for example, national food consumption habits, or that are adapted to national registration for a specific purpose of this use of a veterinary drug, that is maybe only allowed in this country. So there may be additional exposure sources in a specific country that only that country can take into account, that cannot be taken into account if we have to give a recommendation on the international basis. Moreover, what this model basket reflects and the ADI reflects is a chronic exposure. We are not talking about somebody who eats half a beef on one day because there is a big wedding party somewhere, excuse me to talk like this, but just to say what we

are trying to do here is to get a conservative – in a public health protective way – a model that is sufficiently protective over a lifetime exposure. And I think that are most of the comments I wanted to make now. Thank you.

Chairman

274. Dr. Wennberg.

Dr. Wennberg

275. Yes. I have two more comments to make on this. The first one is on this model standard food basket. It is internationally accepted; it is also used in the EU. And the second comment is that the studies performed in the field trials which were evaluated by JECFA reflect the use of these products also in combination, if it was the case that these were the authorised uses in the particular country. So for the endogenous hormones, the combination in terms of the exposure was evaluated, and the additional exposure, based on the use of these hormones compared to the endogenous one in relation to the ADI for each of the substances was calculated. So I do not consider that JECFA only looked at one single hormone in one single instance. The ADI is of course specific for each substance, because there are specific endpoints which have been used for the establishment of the ADI with the no effect level. So you cannot combine different hormones which have different endpoints in terms of toxicology and say that you can lump them together and say that if I use this and this and this I get an increased toxicity. You have to look at each of the hormones and their endpoints, which is what the ADI is based on, to see whether there is a risk to public health or not.

Chairman

276. Thank you. OK. EC please.

European Communities

277. Mr. Chairman, I don't want to become polemic, but I think in the documentation of JECFA and Codex which we have seen, toxicological data, and the evaluations of combinations of implants have not been performed, as far as we know, not for all the substances which we are talking about here. So if the representative of Codex and JECFA think otherwise, we would like to see this paper. We have asked the United States and Canada to provide this paper; they didn't give them to us. So if they are claiming something, we need to see these studies, toxicological and residue studies, where they claim that the combinations of implants, where more than one hormone is contained and administered, has been performed. As far as we know they have not been done, not for all of them. If you allow me to come back on the first question replied by Dr. Tritscher, the basket, of course we have a basket similar to what Codex and JECFA have in their evaluation, but the point, I think, that the member of the Panel was trying to clarify is that we eat daily so many food products and otherwise which contain the same substances, or substances which have the same or similar toxicological effects and activities, and these of course are not taken into account. This is what we would like to clarify. There are so many other substances which have oestrogenic activity when they are consumed in food and this has not been examined. I don't know if it is feasible to be examined. I think it is difficult but it is not impossible and probably the countries which have authorized these hormones must have performed this before they authorized it. And later on we will give you precise reference to our assessment where we do mention this potential risk, possibly from these other sources. Thank you.

Chairman

278. Dr. Boobis.

Dr. Boobis

279. I don't propose to get into a long discussion at the moment on this issue, but I would just make the comment, since it has been raised, about the totality of exposure to oestrogenic compounds in our diet. There have been estimates of the total exposure to oestrogenic compounds, and by far the dominant source of those compounds is natural oestrogens which are produced by plants in our diet. These far outweigh the traces of oestrogens from other sources, either natural oestrogen coming from non-treated animals or the presence of growth-promoting hormones used to treat animals. That is not to say I have addressed the question of incremental risk, I assume that will come up later, but just to point out, in terms of the total burden of oestrogen exposure, this is a much broader question than just the hormones coming from beef, it would open up the whole question of nutritional exposure as well.

Chairman

280. If the JECFA representative is not in a position to clarify on the question posed by EC then can I ask the representatives to move on to the second part of the question. Am I right to understand that the second part of the question has not been fully responded?

Dr. Tritscher

281. Could you please repeat the second part of the question?

Chairman

282. Does the ADI take into account all uses of the hormones as veterinary drugs, including for example for zootechnical purposes? Dr. Boobis.

Dr. Boobis

283. I tried to emphasize this, and I think the joint secretariat has made this point, but it bears repeating. There are two different questions here, and we have tried to answer the specific question. The ADI is derived from toxicological information. We can argue about the security of the conclusions, but it does not consider, nor should it consider, exposure or the use patterns. It is based simply on the toxicological properties and the biological properties of the compound itself. You then come up with a health-based guidance value, the allowable daily intake, that is then compared with exposure. And the second question which one might pursue, and I think we have been, is to what extent are all different exposures taken into account, but that is a separate question from the ones on the board, Mr. Chairman, which is that the ADI does not take account of other uses nor should it.

Ms Orozco

284. Total exposure from food then should be taken into account during the exposure assessment?

Dr. Boobis

285. Yes, indeed. That is where it would come in if it was going to be taken into account. It does not come down the left-hand side of Dr. Tritscher's diagram, which is the ADI derivation based on the toxicology, it comes down on the right-hand side, which is exposure evaluation. And then it becomes a risk management question as to how broadly are you going to include exposures other than those that arise from GVP, good veterinary practice, because of course JECFA bases its evaluations on the use of the compound according to good veterinary practice.

Chairman

286. OK. I hope we can conclude the discussion on this question as early as possible. I will give the last chance to EC.

European Communities

287. Chairman, I am afraid we cannot conclude these discussions because we have a number of other questions, but I would agree with the first reply of Dr. Boobis, that the way the ADI is performed by JECFA does not take into account other use of these hormones, like zootechnical or therapeutic use. The claim is that they cannot do it, or they don't want to know that they may be used in that way, fine, but for the purposes of your consideration this is true, they do not take any, and this actually has been said in the reply of JECFA, which if you wish I can read today. The second question is the reply of Dr. Boobis about where exposure from other sources has come in. If the reply of Dr. Boobis were to be true, then what JECFA does is not correct, and I think that the reply is somewhere in between. It is not as clear-cut as JECFA present it or Dr. Boobis would like to present it, because it all depends what these other sources are and what they contain. And if it is biological activity, in this case we speak about carcinogenesis, it has to be taken into account in the first step, in hazard identification, it is not only the in exposure assessment that we need to consider it. So I think we will have the opportunity, if we go down the questions later on, to clarify this instead of dwelling now on this issue in a generic manner. But if you allow me – because my questions relate to the two questions which you have asked, the first before the lunch break and the second now – if you allow me to have three follow-up questions on this.

Chairman

288. Please do that at a later stage, as I mentioned earlier, because I think that the situation may be the same for other delegations too on the other specific questions.

European Communities

289. Well, I think, if you allow, I will ask at least one question of the three I have.

Chairman

290. OK. With the understanding of delegations, please go ahead.

European Communities

291. Chairman, in the reply of Codex to question number 4, for your consideration I only read the first sentence: There is no adopted Codex standard or related text on the risk assessment of residues .... So what is being talked about here – there is no standard about how to do this risk assessment, techniques and how you set the ADI and MRL. These are the methods used and developed by JECFA, but they are not presented in an assembly of an organ for adoption so that they become standards in the sense of the SPS Agreement. They are considered by some committees and JECFA and a few scientists, as they say, they are developed by individual persons who happen to sit on those committees and they thought that is the relevant model. But the truth is, and this is relevant for our case, there are no agreed international standards on how to do a risk assessment in that sense. The other questions I will keep for later on. Thank you.

Chairman

292. Thank you for your cooperation. Is it on a procedural matter, Canada?

Canada

293. I would simply – I did not hear a question there – but I would propose a question too. I think Drs. Boisseau and Boobis both spoke to the last point raised by the EC, on how safety assessments are conducted and the process by which that's done, and I wonder if they had any comments on the EC's last statement.

Chairman

294. Can I give the floor to Dr. Boobis.

Dr. Boobis

295. I think it is not entirely accurate to say that it was a few scientists at JECFA who developed risk-assessment methodology; this evolved out of the National Academy in the US. It has been developed by the International Programme on Chemical Safety and is the cornerstone of risk assessments by almost everybody. The four-step risk assessment paradigm, as we call it, – hazard identification, hazard characterization, exposure assessment and risk characterization – is very very widely use. It has been endorsed by essentially everybody conducting risk assessment on expert bodies. There has been lots of discussion about whether or not this is applicable to veterinary residues. The view widely held is that there is nothing fundamentally different about the philosophy of evaluating risk of a veterinary residue, as opposed to any other specifics about the exposure assessment; one has to work out the residues in meat from treated animals, but that is a technical detail, as opposed to the overall philosophy that underlies the strategy. So I think that it is not accurate to say that this is something that has been cooked up or produced by JECFA in an informal manner, it has been widely validated by many organizations. And in fact I believe it is in the Codex Manual as well, at least allusion to the general principles.

Chairman

296. If Canada's point is not related to the procedural one, can I give the floor to the experts first, because I saw their flags were raised before you did. Dr. Boisseau and then Dr. Miyagishima.

Dr. Boisseau

297. Thank you, Mr. Chairman. I am sorry, but there were many questions in rapid succession, and I wanted to take the floor following the statement by the European Union to the effect that ultimately, there were various utilizations that the ADI could not take into account. I think we have to be fairly precise on terminology, because otherwise we will be going round in circles like this for hours, without getting anywhere. The ADI has nothing to do with exposures, as Dr. Boobis quite rightly said. The ADI does not need to take account of exposures, it is the logical conclusion of a toxicological evaluation. By "toxicology", we may also mean "pharmacology" or any adverse effect. In any case, it is important that we bear this in mind. Now, we must not confuse the Theoretical Maximum Daily Intake (TMDI) with the daily amount ingested which is the sum of the amounts actually ingested from different sources, and we compare, as the joint secretariat said this morning, I think, the amount ingested with the ADI. So we must stop linking the ADI with the amounts ingested, otherwise I can see no way out.

298. Secondly, regarding the standards and the protocol that we have just spoken of, there is currently a cascade protocol, so to speak. We have, today, a general structure for risk analysis and risk assessment. However, it is true that the JECFA applied this risk assessment to the consumer safety assessment of veterinary drug residues, with the exception of antimicrobials, for several years without a detailed assessment protocol – that work has been going on for a number of years within the

JECFA. However, before the work was done, this protocol was perfectly well established in the minds of all those throughout the world who, at the JECFA or EU level (I am thinking of the CVMPs), use the same methods. Moreover, it was the same people working in the different bodies, so we can hardly say today that this work was done more or less according to the mood of the moment. There was a consensus on the way that this methodology for assessing the safety of veterinary drug residues should be applied. It was neither written, nor formally adopted, but the methodology was perfectly operational and universally accepted. Thank you.

Chairman

299. Thank you. Dr. Miyagishima.

Dr. Miyagishima

300. Thank you, Mr. Chairman. I would like to add some clarification as to what is meant by the Codex reply to question number 4. We did confirm that there is no adopted Codex standard or related text on the risk assessment of residues of veterinary drugs. When we call something a standard or related text, that means any text that is part of the Codex Alimentarius. The Codex Alimentarius is a collection of adopted standards and related texts that are there for guidance or for use by governments. In this particular case the Codex relies on JECFA, and Codex uses primarily MRLs as a tool for risk management. Codex in this sense has not attempted to provide guidelines for governments to conduct risk assessment, because JECFA does the business.

301. This is the reason why the document on risk assessment policy and the whole risk analysis framework related to the work of CCRVDF, which is now in elaboration, is not meant for inclusion in the Codex Alimentarius even if after it has been adopted by the Commission in the future. It will be eventually included in the Codex Procedural Manual, because the document describes the way the Codex interacts with JECFA. So the scope of the document has no links with the guidance Codex intends to provide to governments. This is the reason why the Codex replied that there is no risk assessment guidance within the Codex Alimentarius. In other areas such as microbiological risks in foods, the Codex has taken a different approach, and the Commission adopted risk assessment guidelines which have been included in the Codex Alimentarius. But with the approach the CCRVDF has taken, and the Codex Commission has taken so far, there has been no need for providing guidance to governments directly in terms of risk assessment techniques. Thank you.

Chairman

302. Thank you. EC – sorry, I forgot that the Canadian delegation has raised its flag. Canada.

Canada

303. Thank you, Mr. Chairman. It is always illuminating and interesting to listen to my friend Mr. Christoforou, so I didn't want to deprive him of the podium. But I think, as this exchange demonstrated, in fact it was immediately after the intervention of my American friend who put the statement into the form of a question, we can actually have a very fruitful contribution from the experts when instead of making statements and arguments we put simple questions to them. And I hope that my EC colleague will respect your guidance and in fact your initial statements about the way this process is to be made, which is that at this point instead of making arguments it's better to simply put clarification questions. And if later on, on Monday and Tuesday, we have arguments to make, we will make them. Thank you.

European Communities

304. Chairman, there are two clarifications, and I will not continue this now. It is another thing to speak about the four stages of risk assessment to which Dr. Boobis has referred, risk identification, risk characterization, dose exposure, risk characterization, that is true. But here we were not talking about these four steps of what is a risk assessment and how to do it, we were talking about the ADI, and the maximum limits. For this concept Dr. Boisseau says there were a few scientists, it was probably already before considered and was taken into account in JECFA, but there are no internationally agreed standards about this concept. This is what I want to clarify. The question was relating to ADI and MRL not only four steps. With this we agree, of course, and we claim we can follow these four steps of the risk assessment, but that was not the point, if you allow me to clarify. The second question is: Dr. Boisseau himself has said there are no agreements to the national standards, in JECFA or otherwise, how to define this concept of ADI and MRL. There are questions one may ask about the details or some other important aspect of this, so that is what I wanted also to clarify. Dr. Boobis said that it all started from the United States National Academy publications, this is all fine. But for you to understand, there is the Codex Alimentarius Commission, which is the members of the committee adopting texts, where the four steps of risk assessment have been presented and have been adopted and have been accepted. That's fine. But in JECFA there is no plenary of members of the WTO, for example, where they meet, and they take the papers of JECFA, and they say yes, they are well done, and we accept and adopt them. This does not exist in JECFA. And all these papers, as I said, they are publications without legal status in terms of the SPS Agreement. I think that it is as simple as that, I don't want to confuse the scientists about this, and I certainly would agree with my colleague from Canada that we would have the time to clarify this on Monday and Tuesday; simply then, on Monday and Tuesday, the experts will not be here, so we need to take advantage of their presence here as well. Thank you.

Chairman

305. I would ask the representative of JECFA to respond to that question, not in the context of the legal analysis of the SPS Agreement, but in the context of the work you are doing in JECFA and Codex. I give the floor to Dr. Tritscher.

Dr. Tritscher

306. Thank you. Again, it's not correct the way it was just presented by the representative of the EC, because specifically the ADI concept, how it is defined, and how this arrives, and how to go about to get to an ADI, is exactly described, as I said earlier, in the Environmental Health Criteria document No. 70, Principles for the Safety Assessment of Food Additives and Contaminants in Food. This is the document that was elaborated by a large group of international scientists convened through the International Programme on Chemical Safety. It is a consensus document of an international independent expert scientific panel published in 1987, and this is the basis on how to derive an ADI. An ADI cannot be derived if you don't follow the risk assessment steps as they were defined, so you cannot disconnect an ADI from the risk assessment procedure, the defined steps of hazard identification and hazard characterization. So again, this was not a correct statement. You cannot devise an ADI without following risk assessment steps. Generally this is the basis, and any of the national expert bodies, regional expert bodies, use exactly the same principles and the same methodology, let it be the European Food Safety Authority, former SCF committee, let it be the US FDA or whoever. This is the basis for this IPCS document published at WHO in 1987 and every follow-up from this. Going to JECFA – JECFA is not just a handful of people sitting there and having fun. JECFA is a scientific peer review panel, independent scientific experts that are an international peer review panel. Everybody talks about peer review now. So what JECFA does, they use all the evidence that is available, scrutinize and discuss it to come to a conclusion, based on all the available evidence. Again JECFA works on a consensus basis to the extent possible; if it is not

possible there will be a minority opinion presented. That has not been the case to my knowledge in the veterinary drug field; in the 50 year history of JECFA it only happened twice. So it is the highest level expert body in this field that performs a peer review of all available information. And just saying it is a handful of people sitting together doing something, sorry if I am reacting like this, but I find this rather offensive towards the experts that dedicate their time to do this work in the international context for public health protection purposes. Thank you.

Chairman

307. Dr. Miyagishima.

Dr. Miyagishima

308. Thank you, Mr. Chairman. I will be very brief. I just wanted to clarify that there is an internationally agreed document that governs the whole framework of risk analysis within Codex, which is the Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius. This text was adopted in 2003 and is now part of the Codex Procedural Manual that applies not only to the work of the Commission but all subsidiary bodies. And as Dr. Boisseau mentioned, CCRVDF has now finalized the document called Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Food, and this document is awaiting the final endorsement by the Commission. But it does not mean that CCRVDF is now trying to reinvent the wheel; basically this document describes the standing practice applied by CCRVDF from its inception. Of course, risk analysis is a continuing process and Codex is trying to evolve with more fine-tuning about risk analysis, but basically this document describes the ongoing and established practice followed by CCRVDF. In essence, the basic framework of how JECFA does its work and how its work is treated by Codex has not changed substantively since the beginning of the Codex work in this area. Thank you.

Chairman

309. Thank you. I think the replies are good enough for the Panel to clarify all the issues at hand. So now I would like to move on to the next question, that is purely procedural in nature again. The question is: How does the work of IARC feed into the work of JECFA and Codex? How was this done in the case of hormones at issue? May I ask this question to Dr. Tritscher or Dr. Cogliano? Dr. Cogliano.

Dr. Cogliano

310. IARC convenes its own working groups to evaluate the carcinogenicity of various agents. They have evaluations of steroidal oestrogens as carcinogenic to humans, non-steroidal oestrogens as well, and also oestrogen as used in hormone therapy, and oestrogens and progestogens in combination, as they are used in hormone therapy or in oral contraceptives. There is also an evaluation of oestradiol-17β as carcinogenic in experimental animals, and there is an evaluation of testosterone as carcinogenic in experimental animals. IARC publishes those in the form of monographs, and they are available to be used by JECFA or any other body that is interested in making a decision about those agents.

Chairman

311. Has the representative of IARC ever been invited by JECFA to the Committee meetings?

Dr. Cogliano

312. I have not personally been, but Jerry Rice, my predecessor, might have been. I was there for something about expert advice, but I have not been there to evaluate any chemicals.

Dr. Tritscher

313. IARC is also a WHO organization. We invite the IARC representative to JECFA meetings every time when there are contaminants and relevant substances evaluated. We are not talking about food additives in the context of IARC. What IARC does; IARC does cancer classification, so in the IARC assessments the focus is on the carcinogenicity or potential carcinogenicity of the compounds. How the work feeds in was already basically answered. IARC publishes their work in monographs, so does JECFA, and we base – depending on which one comes timely first is the starting point of the work of the other, so we take each other's work into consideration. Thank you.

Chairman

314. Thank you. Dr. Boobis.

Dr. Boobis

315. To expand on that a little bit, when JECFA discussed the hormones, the natural hormones, for the fifty-second meeting there was a staff member of IARC present who was an adviser, a temporary adviser, and we were fortunate that we had access not only to the published reports, but some of the information about to be published, and in fact, if you read the technical documents from JECFA, it was made clear that the IARC evaluation and some of the information they had put together formed an important part of the deliberations of the Joint Committee.

Chairman

316. Thank you. EC.

European Communities

317. Chairman, I have one question to both representatives of JECFA, actually Codex as well, and the International Agency for Research on Cancer. The International Agency for Research on Cancer has classified, as you know, oestrogen and oestradiol in the first group, which is the proven carcinogens of humans, and they have classified the other two in the second category, group 2A and 2B. So I would like to ask JECFA, how it is possible, since they are interacting, these two international organizations, that JECFA comes to the conclusion they are not proven carcinogens – I am speaking about oestradiol – whereas the International Agency for Research of Cancer has come to a different conclusion. I would like to know: is it because they use different data, do they use different toxicological studies, do they take other considerations into account which make for this different outcome? Because I guess you would like to know as we do, since we take the advice of these two groups into account, which one of the two to follow. One says oestradiol is a probable carcinogen, the other says no, there is a threshold, there is no risk. I simplify, but this is the end result. Thank you.

Chairman

318. I see many flags raised, so I will give the floor the JECFA first, and then Codex, and then Dr. Boobis.

Dr. Tritscher

319. Thank you. There are many things mixed up now in this statement. So JECFA and IARC are doing two different things. First of all I have to clarify that JECFA never said oestradiol is not a carcinogen, you will not find this anywhere in any JECFA publication. IARC does, as I said, cancer classification; it is a totally different thing than what JECFA does in doing risk assessment, and my colleague from IARC will explain what it means, what their work really means to cancer classification. A compound being a carcinogen does not preclude it from a safety assessment being performed and an acceptable daily intake or tolerable daily intake being set. Again, those are not mutually exclusive things. Sorry, let me say it like this: JECFA has evaluated several compounds that have carcinogenic properties and have still been able to set an ADI or a TDI.

Ms Orozco

320. Sorry, can I interrupt you there for asking you for an example of other compounds in a similar situation.

Dr. Tritscher

321. Contaminants in food like the chloropropanols for example, monochlorpropandiol and DCP. I think I will leave it at that in the interest of time, because I know that ...

Chairman

322. Thank you. Dr. Miyagishima.

Dr. Miyagishima

323. Simply to say that there is no standing or institutional linkage between the Codex system and the IARC. Of course, to the extent that the work of IARC is beneficial to the work conducted by the Joint FAO/WHO bodies, such as JECFA, it is up to JECFA to draw any useful elements from the work of IARC. But there is no direct link between Codex and IARC. Thank you.

Chairman

324. Dr. Boobis and Dr. Cogliano.

Dr. Boobis

325. Well, it is just to emphasize the point that in the view of JECFA it is necessary to consider the mechanism and mode of action for the carcinogenicity, because, as we alluded to earlier, there are many different ways in which one can generate a tumorigenic response. I am sure tomorrow we will discuss exactly how oestrogens cause cancer, but as a philosophical point at the moment, just to clarify the point that Dr. Tritscher made, simply because a compound causes experimental cancer in an animal, or even at high doses in humans, does not necessarily and automatically mean that it is not possible to establish a safe level of exposure. JECFA sought to do that for the hormones. One can argue whether it came to the right conclusions, but it was on the basis of consideration of the mode of action and the mechanism of the carcinogenicity. As already stated, at no point did we ever exclude evidence which was readily available at that time, in 2000 and 1999, that in humans at certain levels of exposure oestrogens could cause cancer in endocrine sensitive tissues.

Chairman

326. Thank you. Dr. Cogliano.

Dr. Cogliano

327. I put my flag up just to make one correction. IARC has classified oestradiol 17β as possibly carcinogenic based on sufficient evidence in experimental animals. The agents that are known to be carcinogenic in humans are the steroidal oestrogens, non-steroidal oestrogens and various oestrogen-progestin combinations as used either as birth-control pills or menopausal therapy.

Chairman

328. Thank you. EC.

European Communities

329. Chairman, I think it would be useful if we take a little bit of time on this issue, because it is interesting to know the scientific basis upon which the International Agency for Research on Cancer re-examine partly the same documentation that is available, the toxicological studies and the profile in the mode of action in these substances. And I understand by reading the International Agency for Research on Cancer monographs that they consider that oestradiol, oestrogen and oestradiol-17β not only act through receptor mediation but also they consider them to be genotoxic. This problem, this toxicological assessment of this substance and the other natural hormones – I need to clarify, the International Agency for Research on Cancer, it has not examined the synthetic hormones, but they have examined the three natural. Partly the same studies have been evaluated by JECFA as well, and as you see, they dispute, they go through – if you take and read the opinion of JECFA and Codex subsequently, which is taken out and published – they go through the data, but the ultimate conclusion is that oestradiol has a genotoxic potential, but they do not define it as genotoxic in the sense that the evidence is sufficient. As Dr. Cogliano has said, they thought the evidence was sufficient to define as carcinogenic in humans. So I am still wondering and I would like, as a lawyer, and I hope you as well, to know why on this crucial aspect the International Agency for Research on Cancer comes to a different conclusion for oestradiol, and they also come to different conclusions for progesterone in particular and testosterone as well, than the conclusions obtained by JECFA. I am not trying to fudge the issues, no. But the truth is that part of the scientific documentation is examined by the two bodies, and the conclusions and toxicological conclusions they reach are very important, and I have the feeling, and we have the feeling here, that they are not getting to the same conclusion on that aspect. Dr. Boobis said that he does not, JECFA does not dispute that oestradiol is carcinogenic, fine, but the method by which we define oestradiol as a possible human carcinogen is also important, and I hope it is clear what I am asking the two or the three delegates to clarify. Thank you.

Chairman

330. The Panel's intention in putting forward these questions was purely procedural, as I mentioned, and I think the comment you made is rather stretching out to the substantive issues to be discussed later on, in due course, through exchanges of questions and answers on different issues. I hope we can conclude discussion on this question here and then come back, if necessary, in due course. OK. Then the next question of the Panel is rather broad in concept, or which may capture the broader picture of the issues at hand. The question is: how much scientific evidence is needed for a valid risk assessment? What is normally done if data in a specific area are incomplete? How is scientific uncertainty addressed? The floor is open to any expert to respond. Dr. Boisseau.

Dr. Boisseau

331. Thank you, Mr. Chairman. There are two hypothetical possibilities here: either the necessary scientific data is lacking to the point where the risk assessment cannot be completed – in which case the required data is requested so that the risk assessment can be continued; or a committee, the JECFA – but it could just as well be the CVMP – considers that the necessary data has been gathered and is available, but since there is an element of uncertainty in any piece of scientific data owing either to the experimental protocol used or the obsolescence of the method used, or with the number of animals involved, it uses safety factors to ensure that the evaluation results in proper protection of public health. Thank you.

Chairman

332. Thank you. Any other additional comments from the experts. If there are no follow-up questions from parties, then can I move on to the next, please. Madam Orozco.

Ms Orozco

333. I would like to ask a follow-up question, because I am not quite sure. The question has two elements that we would like to clarify: What would be the procedure when the data is incomplete? And what would be the procedure when there is uncertainty about the science?

Chairman

334. Dr. Tritscher.

Dr. Tritscher

335. Again, very quick, to the completeness of the database; if you want to look at chronic intakes or setting an ADI of course you need sufficient long-term studies that allow an extrapolation or an assessment of the compound. If it is a compound like the hormones, with hormonal effect, you would definitely require reproductive and developmental studies to check specific effects. Again, what Professor Boobis mentioned a couple of times already is that JECFA puts great emphasis on the mode of action of the compound. That's part of the first question, sorry that I am going back, but then the rest is better understood. To the question how much scientific evidence is needed, it is not a check box, it is not a list that then is then just checked off. There are certain basic studies that need to be available; over and above that, it is on a case-by-case basis. Depending on the toxicological profile or the suspected profile of the compound, you would require certain studies. If these studies are not available, if there are significant – now I am going to the follow-up question – if significant data gaps are identified by the Committee, then these have to be clearly identified. For example, there is concern for reproductive effects, however there is no reproductive study performed, that would preclude a safety assessment on that compound, and it would be clearly identified what the significant data gaps are, and the conclusion would be that there cannot be a safety assessment performed on this compound if there is a significant data gap. If the data gaps are considered to be minor, in the sense that a safety assessment could be performed to still be public health protective, however additional data would be required, then there is the option to set a temporary ADI, and then there would be a specific definition of what additional data would be required in order to fill these minor data gaps. A temporary ADI usually has a limited lifespan, meaning the data requirements would have a date attached to them. If a temporary ADI is set, so minor data gaps that are clearly identified are there, then what usually happens is that there are additional safety factors, uncertainty factors, added on to have an extra level of safety added and to take this additional uncertainty into account. Thank you.

Chairman

336. Dr. Wennberg and then the EC.

Dr. Wennberg

337. Thank you, Mr. Chairman. Just short on the residue part. I already alluded to the requirements related to the data needed to perform an evaluation of the residue in the animals in question. When I was talking about how to set MRLs – I am not going to go into that any further – and similarly applying, which I also mentioned before, is that if there are minor gaps in the validation of the analytical method to be used in residue control, for example, JECFA could consider to set temporary MRLs, but we already talked about that.

Chairman

338. EC.

European Communities

339. Chairman, two brief statements and I think we can be more concrete. If you look at the 1987, 1988 evaluation by JECFA of the three natural hormones, they thought at the time that they had a complete set of data, they made the evaluation, but they did not fix an ADI because they thought the data was complete and there was no risk, because of the wide margin of safety, as they call it. JECFA has re-evaluated the three natural hormones again in 1999, and they came to a different conclusion, that this time it was necessary to fix an ADI, because data apparently changed, were more complete. Now, the United States, in its reply to the comments made by the experts and by the European Community, interprets why JECFA fixed in 1999 an ADI is because the data were now complete. This is the terminology, I can find the correct quotation if necessary. Whereas the reply of Dr. Boisseau, why they fixed an ADI for the first time in 1999, is in order to be more convincing. I can find the correct quotation as well. So there is quite an uncertainty in the way JECFA proceeds. The point is, and this comes to the second question asked by Madam Orozco – practically there is no room to take into account uncertainty in JECFA, because they think that they can address uncertainty through the so-called safety factor. By applying the so-called safety factor, sometimes it's 100, 200 or 1,000 times, they think they can take into account uncertainty in the data, but at least the way we understand scientific uncertainty is different. And I would like to know instances where – if there are, there are really very few, very very few in the history of JECFA – where they came to the conclusion that for a substance we do not have sufficient data to propose an ADI or an MRL. And I should give you another example which is also pertinent in this case, the case of carbadox, and I will only mention it and not go on into the details. We were arguing the data were not sufficient in 1996, nevertheless JECFA proposed a provisional, as they call it, a provisional ADI and MRL, and ten years later on Canada, for example, has agreed that the data were not enough and were wrongly interpreted. So I think these questions are very important. Is there any room in the JECFA procedure and the risk assessment to take into account scientific uncertainties what the real scientists understand what is scientific uncertainty? And our feeling is that there is very limited room for that and I don't thing they actually do it. Thank you.

Chairman

340. Thank you. US.

United States

341. Thank you, Mr. Chairman. I again had a very difficult time discerning a question in the last statement by the EC, but there were quite a lot of factual assertions made in the course of that "question". I was wondering if, maybe we could open up the EC's comments to the experts who have spoken on the issue of ADIs and the JECFA/Codex/IARC work. So I would propose that Doctors Boobis, Boisseau, Cogliano and Dr. Tritscher respond to several of the factual statements made by the EC in its last comments.

Chairman

342. Well, before I give the floor to the experts, may I remind you again this is the session for the Panel to put the questions, and we are allowing the parties to ask additional questions in relation to those questions posed by the Panel. So we are not going to make any statements from the Panel or from the parties at this particular moment, and I would urge the delegations to refrain from making any statement and rather focus on the questions put forward by the Panel and replies given by the experts. With that I will give the floor to Drs. Boisseau and Boobis.

Dr. Boisseau

343. Thank you, Mr. Chairman. I will try to keep my reply to the EC intervention brief. Science is a discipline which is constantly evolving. When we manage to resolve a problem, we generally find that there is another problem hidden behind it, and so on ad infinitum. The assessment of the safety of veterinary drug residues is a pragmatic system, because the proper use of veterinary drugs depends on its conclusions. We need to be able to decide, at any given moment, whether we should think of reconsidering an assessment in the light of scientific developments. But we cannot constantly delay that decision, or otherwise it can turn into a Sisyphean challenge. When the EU speaks of these scientific uncertainties, it is the general protocol that is being called into question. We must understand that the committees, the JECFA and the CVMP, work on the basis of the data available. Where do these data come from? Generally from the industrialists that provide them. In the end, there is very little, relatively speaking, in the way of data, from independent bodies. So ultimately, it is going to be necessary, in the light of the information available – if it is sufficient – to make proposals that it will be up to the Codex to accept or reject. If not, none of what we call old molecules will ever be evaluated and they will have to be withdrawn from the market, since no one will support them. The same applies to the developing countries. There are substances which are very important for the developing countries, but which represent a minor market. Most of the time, although their files are not complete the JECFA tries to conduct these evaluations on the basis of the data available and using appropriate safety factors to recommend ADI and MRL standards to the CCRVDF, that guarantee public health. Thus, I think it is important to remember that the approach is a pragmatic one.

344. As regards what happened in the re-evaluation of natural hormones in 1999, I maintain what I wrote, namely that during the preceding re-evaluation, the margin of safety between what might have been envisaged as an ADI and the daily amount ingested seemed to the JECFA to be such that it did not appear necessary to determine ADIs, and its conclusion at the time was: ADIs not necessary; MRLs not necessary. It emerged that there was a problem of communication, because as a result this margin of safety did not appear; and the JECFA, of its own accord – this was not requested by the CCRVDF – reverted to this evaluation, for which, in fact, it had access to a whole data package. Please excuse me, I made a mistake in my previous reply: there were indeed new data in connection with the data package which the FDA placed at the disposal of the JECFA, and which helped, as it were, to determine more precisely this margin of safety between an ADI that was established at that time and the theoretical daily intake of residues. The JECFA once again determined that it was not necessary to establish the MRLs since the margin of safety was still sufficient. In other words, the

evaluation remained unchanged, and it is not really the availability of new data that led the JECFA to reconsider its previous evaluation – it was only that the JECFA wanted to be more transparent, more explicit. The CCRVDF did not want to take account of this new re-evaluation which yielded the same results and which it had not itself requested. Thank you.

Chairman

345. Thank you. Dr. Boobis.

Dr. Boobis

346. Just from my own personal perspective, and I am not necessarily speaking for JECFA or anybody else here, I think it is probably fair to say that when conducting a risk assessment, we are not really looking to see if a data package is complete as to as much as whether it is adequate for the purpose, because I agree entirely with everything that Dr. Boisseau has just said, that science moves on, and it would be complacent for a risk assessment body to assume that it knew everything about a substance at a particular point in time. We have to work within the available information, and the question we ask is: do we have sufficient information at this point to conduct a risk assessment? – not: is the data complete and are there no scientific questions remaining to be answered. And I would add that there are numerous examples in the JECFA monographs of substances where it was not possible to establish an ADI on the basis of incomplete data; that has been done on several occasions.

Chairman

347. Thank you. Dr. Tritscher.

Dr. Tritscher

348. I would like to comment on the aspect of uncertainty and if or if not uncertainty is taken into account by JECFA assessments. It is correct that scientific uncertainty is difficult to quantify very often, and the scientific community is still debating. There is a lot of debate currently going on to better quantify uncertainty in the database, to give a better information to the risk manager as to the confidence on the conclusions that are reached. As the delegate of the EC said, real scientists even have problems to define scientific uncertainty. The experts working in JECFA are also real scientists and they also have problems with that. However, it is always taken into account and, very briefly, there are two aspects that need to be separated out, that is uncertainty and variability. Uncertainty is what we don't know, and variability is variation in a response between individuals, between species. Those are two different concepts and both need to be considered. Uncertainties as to extrapolations from model systems to the real-life situation and so forth, they are taken into account by safety factors that are also called uncertainty factors. Now there are default factors that have been used by everybody, by all the expert bodies since the inception of the invention of the ADI, and now increasingly efforts are undertaken to go away from default uncertainty factors to data-derived uncertainty factors, meaning to put more science into the derivation of these factors to take account of true uncertainties, if possible, if the data are available. That is the concept of the chemical specific adjustment factors. Again, a concept that was developed by Andy Renwick, I think, originally, but the International Programme on Chemical Safety has published on that and the Expert Committees like JECFA and JMPR are trying to apply this concept where possible, meaning where data are available to extrapolate, for example from the animal to the human situation. So it is factually entirely incorrect to say that JECFA does not take uncertainty into account. Thank you.

Chairman

349. Thank you. I think the comments just made by Dr. Boobis and Dr. Tritscher have already answered the Panel's next follow-up question, but I would appreciate it if any other experts would further elaborate on this particular question, that is: how would you distinguish between insufficiency of science evidence and scientific uncertainty? Could you rephrase your comments in more clear terms to distinguish between these two concepts. Dr. Cogliano.

Dr. Cogliano

350. Yes. I want to start by agreeing with Dr. Boobis's comment that it is not so much a matter of being incomplete. But I would also point out that there are several kinds of uncertainty. There are uncertainties as to, for example, what is a null-effect level in animals, or a safe dose; or how would you extrapolate between animals and humans. There are also wider uncertainties about – are the animals predictive at all of humans, or is a single chemical fed to an animal predictive of the human situation? There are very different levels of uncertainty and I think that the way some types of uncertainty are addressed is by trying to quantify them, by trying to get data derived from chemical-specific uncertainty factors. Some forms of uncertainty are addressed by general assumptions, like we will assume animal results are relevant to humans unless we had the data to show otherwise. So that is another approach to dealing with uncertainty, to take a conservative approach and say that we will assume that these study results are useful. And I think that as risk assessment evolves there are more and more questions that are asked. We are now asking more questions; once we understand the mechanisms we start to ask: what is the range of variability in human populations and who is likely to be more susceptible? These are concepts that IARC monographs are trying to address more in the future, but they had not really been questions that were routinely asked 20 or 30 years ago. I think that what we do with uncertainty does evolve over time and there are different forms of uncertainty that do get different approaches. Some are very quantitative and some are much more qualitative. I think I will leave it at that since more specific questions – it's a very broad-ranging field, I think, to try to really answer in a few words. I think there can be whole books written on uncertainty and how to deal with it.

Ms Orozco

351. Simply, if you have similar explanation as to what is or what's not sufficiency of scientific evidence?

Dr. Cogliano

352. Let me try to answer that in the context of the monographs. If we don't have epidemiological studies, good epidemiological studies, we will say we have inadequate information, and then the evaluation will proceed looking at the animal studies. If we have good bioassays, we will make our conclusion that something is probably carcinogenic or possibly carcinogenic or not based on the animal studies. If we don't have good animal studies or good human studies, we have inadequate information, and we would end with saying we cannot classify this substance. So we do want to have either epidemiological studies or animal bioassays. Now let's shift to the mechanism field. If we don't have a good mechanistic understanding, that will not stop us from classifying the substance; we will classify the substance based on the human and the animal studies, even if we do not understand the mechanism. So having epidemiology or animal bioassays, that's a requirement to come up with a classification. Not having mechanistic studies – its nice to have that, it contributes to our understanding, but it does not stop us from a classification. So I guess you could say what we need, and IARC usually has, are some animal bioassays or some epidemiological studies and then we will proceed with a classification. If the rest of the database is somewhat lacking, that does not affect the classification. Now I should mention that IARC does not come up with safe levels of exposure and

uncertainty factors. So our uncertainty analysis is really different from what JECFA would do or someone else trying to come up with a safe level for consumption in foods.

Chairman

353. Let me put this question to all of the experts. If there is scientific uncertainty, would you all agree that there is always insufficiency of scientific evidence, or, even if there is scientific uncertainty, may there be a situation where scientific evidence is sufficient in terms of risk assessment? Dr. Boobis.

Dr. Boobis

354. I will try and answer that question in a slightly different way, if I may, which is just following on from the comments of Dr. Cogliano. Where there is scientific uncertainty, we would tend to adopt a worst case default in extrapolating the data to take account of that, so we will use the most sensitive endpoint in the most sensitive species for the extrapolation purposes of a risk assessment, assuming that it is relevant to humans and assuming that humans are going to be more sensitive than animals. Now that is a fairly conservative assumption, based on the totality of scientific information available to us at this time. The insufficiency of scientific evidence, I would say, as has been indicated, could be trivial, it could be that just one test is not there and we can fill in, but it could be substantial. For example, there might not be a reproductive toxicity study for a compound that women of child-bearing age would be exposed to, in which case we would consider that a major insufficiency of data, not a scientific uncertainty, just an absence of data, and we would not proceed without filling that data gap. So I think they are rather different issues; one we can handle with taking conservative defaults, for the other we really need information to allow us to proceed.

Chairman

355. Thank you. Dr. Boisseau, Dr. Cogliano and then Dr. De Brabander.

Dr. Boisseau

356. Thank you, Mr. Chairman. I am afraid it will be difficult to reply to the question you have just asked. I can repeat what I said, namely that if there is a major insufficiency of scientific data, as Dr. Boobis just mentioned, we cannot go any further in the evaluation of the safety of residues of veterinary drugs. There are other cases where scientific uncertainty with regard to less important data would not prevent a conclusion from being reached with a safety factor that would provide for adequate protection of public health. Beyond that, it is impossible to draw up a table with two columns showing what constitutes insufficiency and uncertainty. All we have is specific cases, we can provide the odd example. We could speak of insufficiency in the case of suspicious results of short-term mutigenicity tests without a supplementary carcinogenicity test or without any studies involving radio-labelled elements for a tissue depletion or a metabolism study. That is an insufficiency. We can give you a few examples, but there will always be cases that do not fit the examples. The reply that I am tempted to give you is that a distinction must be drawn between an individual evaluation, whatever the competence of the expert involved, and a collective evaluation conducted by a committee of competent experts, be it the JECFA, the CVMP, or another committee. We must not underestimate the notion of collective evaluation. When 30 or so experts reach a consensus that there is an insufficiency of data or that a scientific uncertainty can be managed through safety factors, I think that we can be fairly confident – this is a collective approach.

Chairman

357. Thank you. Dr. Cogliano.

Dr. Cogliano

358. I was going to respond. I think similarly – it really depends on what the question is, for example: does tobacco cause cancer? I think the answer is unequivocally yes. Are there uncertainties or are there things we don't know, for example I was asked the question earlier, am I going to get cancer if I smoke for only five years, or only one year, or only two cigarettes a day? We don't really know exactly the shape of the dose-response curve. But we do know enough to know that from a public health point of view tobacco is definitely harmful and we should take steps to curb smoking. There are always going to be uncertainties or things we don't know at the fringes. What happens if we smoke and we also work in a dusty environment, what happens if we smoke and we have vitamin deficiencies, these are the niceties that scientists will say are uncertainties, and there are things that we would like to know more about. So I think when you are asking about insufficiency of evidence it is really: insufficient for what purpose, and what is the question you are trying to ask? In some cases the data set can be absolutely conclusive that tobacco is harmful, but without necessarily answering every single question: what about in combination with this or in combination with that or two cigarettes a day? So yes, keep in mind the purpose, and data sets are always sufficient to answer some questions and there is always more that you could know if you wanted to answer everything.

Chairman

359. Thank you. Dr. De Brabander.

Dr. De Brabander

360. Thank you, Mr. Chairman. As you know, I am layman in that area of risk assessment, but in answering this question I really want to make some remark on a question which is important to me and perhaps for the whole system. I agree that science grows continually, we always have new evidence. I also agree that there are internationally recognized items to make the risk assessment for veterinary drugs, but when you as a human being take medicine, or you give a veterinary drug to an animal, it is in order to cure it from a disease, and when you take a medicine, you always balance the profit of taking a medicine against the risks, because every medicine has its side effects, against the profit of being healed. So the question I ask: by scientific uncertainty, if you are using hormones, what is the counterbalance of using hormones except of profit, money?

Chairman

361. Thank you. Any other – EC.

European Communities

362. Thank you, Chair. A simple question. In the view of all experts, perhaps, and whoever wants to reply on this: is direct genotoxicity of oestrogens an issue on which there exists scientific uncertainty?

Chairman

363. The floor is open. Dr. Cogliano.

Dr. Cogliano

364. Yes, I think there is scientific uncertainty. One of the exhibits you have was the summary of the most recent monograph meeting on the oestrogen/progestogen combinations, either as birth-control pills or as menopausal therapies. And as I mentioned earlier this morning, a hormonal

mechanism is clearly operating, but there was some evidence that there could be genotoxicity operating; it's not as strong. It was not the entire working group that put a lot of credence in it, but enough members of the working group thought that there was some possibility of genotoxic action that our summary does have a paragraph for each of those two types of exposures that mentions that there could be some genotoxic activity as part of the cancer mechanism. I think that is an area of continuing research and obviously more will be known later.

Chairman

365. Thank you. Dr. Guttenplan.

Dr. Guttenplan

366. I think qualitatively one can say that there is very little uncertainty in the fact that oestrogen is genotoxic, however quantitatively I think there is a lot of scientific uncertainty. I don't think we can really estimate the risk at this point from such low levels of genotoxic effects.

Chairman

367. EC.

European Communities

368. Mr. Chairman, I think that this is a very important question and we may replicate the examples where we would like to ask the scientists, all of them, where there is scientific uncertainty and where it comes from. Does it come from the lack of sufficient evidence, as you say in your question, or does it come from, as I would put it, from evidence which is there on the table but it is conflicting? One does not agree with the other evidence? And I think there is a very important causal relationship between these two concepts. Our suggestion is – and I would like to see if the experts agree or disagree – we would say, and we have said in our submissions to the Panel, if the evidence is insufficient, then I think practically always there will be scientific uncertainty, because the evidence is not sufficient. Dr. Boobis has said: if it is a major insufficiency; but it is a value judgement, whether the insufficiency is small, higher or major. Our suggestion to go about this issue is, if the data are not sufficient, there is scientific uncertainty. But this is not all, and it is not the most important in this case as well, because as Dr. Cogliano and Dr. Guttenplan have said, qualitatively there is no doubt that oestrogens are genotoxic or carcinogenic, but the evidence is not sufficient in terms of quantity. And there we will also propose to the Panel – and if the experts agree or disagree they can say so – but when there are conflicting interpretations of the evidence that is available, still we will argue that there is scientific uncertainty. Thank you.

Chairman

369. Thank you. I think the EC's comments are somewhat related to the questions that the Panel are going to put forward later, so I would appreciate it if the experts would respond to the EC's comments when they respond to the Panel's questions, and then I will give the floor to the US.

United States

370. Thank you, Mr. Chairman, I want to interject. I feel with the last question from the EC we have strayed into the scientific evidentiary discussions of tomorrow, and I just wanted to raise that point clearly. The EC's assertion that these hormones function by a genotoxic mechanism at relevant exposure levels is critical to their arguments, and I would propose either the United States can go

forward with its questions on genotoxicity and the scientific evidence, or that we hold back until tomorrow at the time the Chair had set aside to discuss the scientific elements of the case.

Chairman

371. OK. In connection with that comment, may I propose to the delegations: why don't we go through all the Panel's questions as quickly as possible, and then based upon the answers and replies and comments from the experts on all these questions put forward by the Panel we can have more structured discussions by the parties, more elaborate questions on these basic discussions. So that we do not duplicate or repeat discussions we had already. I think that would be a more structured way of debate for today and tomorrow. So I would request the understanding of the delegations by way of refraining from putting many additional follow-up questions on the issues at hand. Are there any comments or replies from the experts? Dr. Boobis.

Dr. Boobis

372. I appreciate your comments, Chairman, and will not enter into discussion about the evidence. I just wanted to make a general point, which is that it would be a mistake to think that risk assessment results in the complete and absolute agreement of everybody in the risk assessment. The nature of the evidence available on science in general is such that we will never get a uniform interpretation. What happens generally is that there is a consensus and if necessary the adoption of defaults which are conservative to allow us to move forward. Seeking unanimity on the interpretation of all the data is futile because it will not happen.

Chairman

373. Thank you. Let me put the Panel's next follow-up questions, two questions at the same time. The first is: at what step in a risk analysis is a determination made whether the available evidence is sufficient to undertake a risk assessment? The second is: at what step of risk analysis does one factor in the level of protection to be achieved by an SPS measure? Any expert? Dr. Boobis.

Dr. Boobis

374. Could I just ask you, Chairman, to repeat the second half of that question?

Chairman

375. The second one is: at what step of a risk analysis does one sector in the level of protection to be achieved by an SPS measure? I would rephrase the last part of the second question as: by a health protection measures, instead of SPS measure. Dr. Cogliano.

Dr. Cogliano

376. I would actually still like to clarify that. It seems to me the level of protection is something that was discussed earlier as part of risk management, and I am not sure that it is part of the risk assessment. Well, risk analysis, then, is a new term we have not talked about. We have talked in terms of risk assessment; is risk analysis being used to mean risk assessment?

Chairman

377. I don't want to go into the detailed legal issues which will be the focus of our discussion next week, but there is a difference in the terminology of risk assessment and management, and there is a

broader concept of risk assessment, risk analysis, so I think it would be better to avoid that discussion at this time, and I give the floor to Dr. Tritscher.

Dr. Tritscher

378. So at what step in the risk analysis is a determination made about the sufficiency of the data to undertake a risk assessment? In the ideal case you would have a step that's called problem formulation, when you really formulate the question, what is the concern, what is the question that the risk assessor should answer, which is followed. Now, there are different terms used – a preliminary risk profile – this is a step where you really look what kind of data are available. Now in the international field, in the context of JECFA and Codex, these steps have not been formalized as such, not in that level of detail, the way I have just described it. What happens is, the Codex Committee, CCRVDF, poses fairly simple, if you allow me to say it that way, a simple questions to JECFA, asks JECFA to perform a safety assessment or a risk assessment on a specific veterinary drug when used according to good veterinary practice. And at that point it goes over to the risk-assessment body, and the risk-assessment body, JECFA in that case, puts out a call for data and performs literature searches, the experts perform literature searches on all publicly available date. Now in the concrete case of JECFA, in the preparation of the meeting, a designated expert reviews the available database and prepares what we call a draft working paper as a basis of the discussion of the Committee at the meeting. If at that point the expert determines that the data are insufficient to allow an assessment, that would be recorded as such, and why the insufficiency is there, or what other significant data there is. So the working paper would lay that out, and then, when the actual JECFA meeting takes place, the Committee would discuss that as such. So to answer the first question, in the context of the JECFA/Codex system – in what step of the risk analysis paradigm – in this case it is at the risk assessment step. So JECFA makes that decision if the database is sufficient, as it concerns us, as opinion of an international expert panel.

379. At what step of the risk analysis does one factor in the level of protection? Now the level of protection is a term that comes from the microbiological area and is not as such used that much in the chemical area and in the context of chemicals in food, also veterinary drugs we are now talking about, where the risk assessment is performed to set an ADI. What that actually means, what an ADI is, what is done is to set a level of no apparent risk on the basis of the available data. So it is a little bit like an acceptable level of protection, like some other agencies or authorities or expert bodies do, in a sense, that one additional cancer case in a million population would be an acceptable level of risk. This is clearly a risk-management decision. The risk manager would have to define this for the risk-assessment body, to go to a certain level of protection. If we are talking about an ADI, setting of an ADI, this is not the concept. What the concept behind there is, to set – again, I repeat – a level of no apparent risk. This is a chronic acceptable intake level without – this famous term – appreciable health risk.

Chairman

380. Thank you. Dr. Miyagishima.

Dr. Miyagishima

381. Thank you, Mr. Chairman. I will speak only to the first question because I still have some difficulty in understanding the meaning of the second question. The determination, or any judgement as to the sufficiency or insufficiency of data to undertake risk assessment, may well take place within the risk-assessment programme. For instance, JECFA may come to a conclusion that the scientific data is insufficient to undertake a complete risk assessment, and they may abort their undertaking at that stage. There are also cases where the risk managers, in this case the Codex Alimentarius Commission, may already foresee the insufficiency of scientific data and yet the Commission may

still ask the JECFA to attempt to undertake a risk assessment, or the Commission may decide not to waste the resources of JECFA and opt for another risk management options that would not require stringent risk assessment, for instance the development of a code of practice, rather than numerical standards, could be an option. There may be other options. I must say that there are cases where risk managers make some judgements on this point. Thank you.

Chairman

382. Thank you. Then could you also explain what a deterministic approach to risk assessment is, and what other approaches are there? And in relation to that: what is a so-called hazard-based approach, and under which circumstances is that approach used? I would welcome the replies from the experts to these comments in combination. If there are no specific – Dr. Tritscher.

Dr. Tritscher

383. I can try to give you the very very brief description, but there are also written comments to the deterministic versus probabilistic, if this is what is meant in this sense. I am sorry, but sometimes it's not that clear what is really behind the question. Deterministic approach to risk assessment means that we are using point estimates – high-level consumer, mean-level consumer – on the exposure assessment, individual points on the dose-response curve, whereas probabilistic takes distribution into account – like I explained earlier, you have variability in responses, and to take this into account is a much more complex way of doing risk assessments. I am not aware that even on the national level really probabilistic risk assessments are performed. This is highly complex and is not routinely done. Increasingly probabilistic exposure assessments are done, meaning where one takes into account the variation of levels of different chemicals in food and the variation of consumption patterns, variation in portions of what people eat. That is increasingly taken into account; whereas when it is just a point estimate, what is the mean level of occurrence, what is the mean portion size. Taking also probabilistic approaches into account on the toxicological side, if you would think about the graphs that I had, so that, going down the left arm of the graph, taking also distributions into account is highly complex and definitely not done routinely, and – other than, let's say, in the scientific experimental field – I am not aware that this is done in the regulatory field. Again, on the international basis, in the context of JECFA we are basically bound to use deterministic approaches, because we basically have to cover scenarios for the whole world. However, again, having said this, the increase in the efforts now, at least on the exposure assessment, we try to take distributions into account. And I do not understand the second question, what is the hazard-based approach. Any risk assessment starts with the hazard, it is the hazard-based approach, so apologies, I do not understand the question.

Chairman

384. As I understand it, that terminology was used by one of the experts or parties in their replies or submissions, which I cannot identify for the moment. Dr. Boobis.

Dr. Boobis

385. Well, I suspect, what Dr. Tritscher has just explained is exactly what I understand by deterministic versus probabilistic, but I have a suspicion that something different is meant here. Obviously we are trying to get to a different place, so that deterministic is where we use point estimates, conservative assumptions, but the underlying assumption, based on analysis of the data, is that there is a point at which one can reach a safe level of exposure, an acceptable level of exposure, and so that is the basis for arriving at an ADI based on point estimates. One could do it in different ways, probabilistic, which is much more complex. But I think that what this is to be contrasted with is the idea that there isn't a safe level of exposure and what one could use under such circumstances is

what is called quantitative risk assessment, extrapolating down levels of exposure, where one gets to a level where there is still a risk, but the risk, in the view of the risk manager, is considered acceptable. Now that is not an approach that JECFA has used before for veterinary drug residues. A hazard-based approach, I would imagine, is a qualitative risk assessment, if you like, where one stops once one has identified a hazard that is deemed unacceptable. So, for example, the compound is shown to be direct-acting genotoxicant; this is considered unacceptable at any level of exposure, permitting exposure would not be appropriate, and then one stops the risk assessment at that point. So it does not need to take account of exposure, because any level of exposure is deemed to be of concern. There are some who argue that certain other endpoints, such as certain types of neurotoxicity, would fall into that category as well. There are intermediate positions, which is that even if there is such a hazard, one could think about what is the margin of exposure, or what is the exposure with respect to the so-called threshold of toxicological concern. These are newer strategies which have been designed to deal with endpoints which may not have a discernible threshold, but where some exposure may be unavoidable, for example a contaminant, and so we have to determine whether we need to prioritize resources to bring exposure down to lower than that. The issue of veterinary drug residues, which are compounds that are added intentionally to animals, is a wider discussion and I won't even enter into that here because it is outside of the thrust of the question.

Chairman

386. I think I did understand the issues but could you repeat once again, but in a much briefer way, the difference between deterministic and probabilistic approaches.

Dr. Boobis

387. I am not sure that that is helpful here, Mr. Chairman. The deterministic approach is to use single estimates of, for example, the toxicological no observable adverse effect level, the exposure level etc. One uses conservative assumptions for those values. The probabilistic approach is to take distributions of those values and try to get closer to the real world situation. We are not all exposed to the highest level of residues our entire lifetime and with the sensitivity of the most sensitive animal, and the most sensitive endpoint. So we can use distributions of those values, multiply them together, and say the probability of an individual lying on the curve is X, very low, medium, high, whatever. And then that requires the risk manager to take a decision as to a percentile of the population they wish to protect, because you never reach a 100 per cent on a distribution curve.

Chairman

388. Thank you. If there are no other follow-up questions, let me put the next question. If a substance is genotoxic, can a threshold be established? If there are any substances for which no threshold can be established, how does this affect the conduct of a risk assessment for such a substance, and what happens to the four steps? Dr. Boobis.

Dr. Boobis

389. There are substances for which there are thresholds for genotoxicity; it depends on how it causes the genotoxicity. For example, it may be acting indirectly through the apparatus that allows cells to divide, the so-called spindle apparatus, which is actually a protein which allows the DNA to segregate during cell division. And it has been shown that inhibition of that process has a clear threshold, and there are some pesticides which have been regulated accordingly. It is deemed that it is possible to adopt a deterministic approach for such compounds, with an allowable daily intake because there is a threshold. Most thresholds are demonstrated experimentally, mechanistically and *in vivo*. Whether there is a threshold can be established on the basis of scientific evaluation of the underlying mechanisms but not just on the observable data. I think it would be fair to say that the

conduct of the risk assessment would depend upon the purposes of the risk assessment. If it was a contaminant, there would still be the need to proceed to determine where is the level of exposure relative to the level of concern. If it was a veterinary drug residue, then one might consider that it would not be acceptable to allow a non-thresholded compound to be present in the diet. But it is very much at the discretion and direction, I would say, of the risk manager as to how one would proceed.

Chairman

390. When it comes to the question of establishing a threshold, what is the difference between a genotoxic substance and a substance with genotoxic potential? When a substance is genotoxic, by definition, and is there any possibility of not being able to set a threshold?

Dr. Boobis

391. Yes, absolutely. If it was shown to be a direct-acting genotoxicant which caused mutation, and there was an indication that that also occurred *in vivo*, then it's very likely one would conclude that it was not possible to identify a threshold. There are one or two rare examples of compounds which are direct-acting genotoxicants, which because of metabolic reasons there is considered to be an *in vivo* threshold, but they are very very rare. As I said before, and as others have said on this side of the table, it very much depends on examination of the underlying data and the scientific interpretation of that data as to where one gets to in considering the significance of genotoxicity, and whether or not one can establish a threshold for that compound. There are no absolutes in this.

Chairman

392. Dr. Guttenplan.

Dr. Guttenplan

393. Most genotoxic compounds that we know of now are of the type that directly damage DNA and cause mutations, and they don't exhibit a threshold. In terms of risk assessment then, the critical factor would be exposure. If exposure is near zero, then whether there is a threshold or not, it does not make a difference, you are not exposed, there is no risk. But determining the exposure is then critical in the case of a compound that exhibits no threshold. Now many of these genotoxic compounds, from what we can determine in animals, do not have, and this was discussed before, a linear dose-response curve. So determining risk from a compound without a threshold, where you don't know the dose response at the low levels, requires a fairly high level of extrapolation, and there is going to be a larger uncertainty, and that is one reason for the uncertainty factors.

Chairman

394. Thank you. Any additional questions from the Panel.

Ms Orozco

395. I would please ask Mr. Guttenplan to repeat what he has just said, because I am trying to think through, and I am not sure that I did understand.

Dr. Guttenplan

396. Well, let me see if I can recapitulate. Yes, the type of genotoxic agent that damages DNA and causes mutations, as opposed to the spindle-active compound that has a threshold, is not going to have a threshold. And then its risk is largely going to be determined by how effective it is as a

genotoxicant and the exposure level. If you are not exposed, or the exposure is very low, then the risk may be insignificant. However – yes.

Ms Orozco

397. Sorry to interrupt, but if I allow you to end, then I will ask you to start again. Exactly this is the point where I lost you. If the premise is that a genotoxic substance can create damage to DNA, why do you say that at low exposures that changes?

Dr. Guttenplan

398. I didn't say it changes. I said that there may be no appreciable risk. We have naturally occurring substances within our bodies that cause DNA damage, they are always there. Oestrogens may be in that class of compounds. We live with this. You cannot do anything about that background. That small amount that comes from a genotoxic agent if the exposure is very low may be insignificant in comparison to the natural background.

Chairman

399. Thank you. If there are no other additional follow-up ... Dr. Cogliano.

Dr. Cogliano

400. Can I try the same thing with an example we had two years ago at IARC, with formaldehyde, and that's again another substance that is carcinogenic to humans. It is genotoxic and there was a lot of discussion about what is the shape of the dose-response curve as you get down to lower doses. And when you have no threshold basically it means your dose-response curve goes down in some shape, but it does not go hit the x axis and be flat. A threshold means your low dose is a flat 0, and then it goes up after some threshold dose. No threshold means that as soon as you leave zero you are going to have some risk. Now, so what Dr. Guttenplan said, at very low doses, you also have very low risk. Now the question is, we don't really know, there is uncertainty about the shape of the dose-response curve at the lowest doses, and this is what came out in the modelling that was discussed at the IARC meeting on formaldehyde. Possibly you could have a dose-response curve that goes linear all the way down to zero. Possibly you could have a dose-response curve that is very steep at high doses and then at low doses it still goes down in a straight line, or you could have something that is curved all the way down but it is still slightly above zero for any finite dose. The point is, we don't have studies that are powerful enough to tell us what is happening at the lowest of the low doses. So there is some uncertainty. But when you have no threshold, it means you are not looking for a dose where you are absolutely safe, what you are looking for is a dose where you have some low level of risk. And you do your best to try to describe that dose-response curve as low as you can, but at some point you still have uncertainty and you cannot with any degree of confidence say what is the shape in this very very low range. Does that help any?

Ms Orozco

401. Up to your last sentence there I got it. You were saying – and thank you for the effort too, to explain this important element – if there is a threshold, it means that a dose that is lower than your threshold does not pose any apparent risk?

Dr. Cogliano

402. That's right. The risk curve is flat up to a threshold dose, and then it begins to rise, so below that dose, yes, your risk is zero.

Ms Orozco

403. So why is it important to know what happens below that dose?

Dr. Cogliano

404. That's if you have a threshold, it's not important to know; but if you cannot establish a threshold, you may have some level of risk, and we were really talking about cases where we cannot establish a threshold and there is uncertainty about whether the dose-response curve is going down with some undefined shape, and how low is that risk at the lowest of doses.

Ms Orozco

405. And when is it that you cannot establish a threshold? Is it because of the mechanism?

Dr. Cogliano

406. Yes, the mechanism gives us clues as to whether something has a threshold. I think it has been stated by a couple of people that a direct-acting mutagen is not likely to have a threshold.

Chairman

407. I think my follow-up question is also related to the question which has been responded to just now. Would you clarify the difference between linear and non-linear situations, which are referred to by the parties? When would it not be feasible to set this threshold below which there is no appreciable risk?

Dr. Cogliano

408. Linear simply means the dose-response curve goes down at low doses at a straight line. Its not a straight line all the way up to past 100 per cent risk, its going to level off. But at low doses, linear means the risk is proportional to dose, and at any level of dose higher than zero there will be a risk higher than zero. Non-linear means the curve has some other shape and that's what is really problematic, because at those low doses, we don't have enough animals or our epidemiological studies are not big enough to observe what happens at one picogram of exposure. With a typical animal study with 50 animals, the lowest you can observe is a 2 per cent risk. With an epidemiological study that's got 10,000 people, the lowest you can observe is the one in 10,000 risk, but you still don't know if there is some lower level of risk at lower exposure levels. So the problem is that when you have a non-linear dose-response curve, you really don't know the exact shape at low doses, and that's where we get into what Dr. Boobis had said; we take conservative assumptions and try to predict what is the worst it can be, because we really can't precisely specify what the risk is there, so we say, well, the highest it could be is this, and then a risk manager has to decide if that is an acceptable level of risk, given all of the other factors that a risk manager thinks about.

Chairman

409. Even in the linear situation could there be a situation where the threshold cannot be established?

Dr. Cogliano

410. In the linear situation we do not have a threshold. Threshold means it's flat at zero and then starts to go up, like a hockey stick perhaps, it's flat against the ice and then it goes up to the person's

hand. Linear means it is just a straight line from the origin of the graph and there is a risk at the lowest of doses. Now that risk can be very very very small, and if exposure is very very very small the risk is very very very small, but the risk is not zero. I think that is the distinction between linear and a threshold kind of response.

Chairman

411. It may be linear, but it never hits the bottom, zero. After all it has to be flat at some point.

Dr. Cogliano

412. I don't think there is consensus that it has to be flat at some point. I think that is one of the scientific arguments a lot of risk assessors have, about whether everything has a threshold or not. I think there is a consensus that there can be low levels where risks are very very low, and some people will say the risks are zero.

Chairman

413. Dr. Guttenplan?

Dr. Guttenplan

414. Yes, the problem is in the second question. That question says: when would it not be feasible to set a threshold below which there is no appreciable risk? And that is the question; what do you consider appreciable? One in a million, one in a thousand?

Chairman

415. Well, actually, that is the Panel's next question (laughter). Let us go directly on to that question: what is appreciable risk, no appreciable risk, no apparent risk, zero risk, no additive risks, no adverse effects – what are the differences between all these terms?

Dr. Guttenplan

416. Lets see all the terms and then (laughing). As far as what is an appreciable risk, I think that is up to the risk management to decide, what they consider appreciable and acceptable. If there are many compounds with additive risk, and if you have several compounds, each has a risk, and each risk is independent, then they are additive.

Chairman

417. But if the appreciable risk is a concept related to risk management rather than the risk assessment, then it could vary depending on the level of protection chosen by each country.

Dr. Guttenplan

418. Exactly, yes.

Chairman

419. Then there would be no objective criteria at all. It could vary from zero to ...

Dr. Guttenplan

420. In performing a risk assessment you can come up with a number, but which number in terms of risk a country wants to use is up to their own individuals, is up to their own risk managers.

Chairman

421. Dr. Boobis.

Dr. Boobis

422. I think part of the confusion is the innate self-preservation of scientists who don't want to commit themselves to absolutes. Most of those terms there generally have similar meanings, no appreciable risk, no apparent risk, zero risk, no adverse effects, maybe not the one no additive risk, we can talk about that later. And I will just try to explain why it is we use this term quite frequently, no appreciable risk. First of all, it is true, the level of protection is set by the risk manager, in that by usage and by adoption there is an implicit if not explicit level of protection for a thresholded residue, and that is how we set the ADIs as has been explained, based on default assumptions on the safety factors that are in common use. This provides, de facto, a certain level of protection. That level of protection, to this date, has been accepted by the risk manager as being appropriate, because they accept the risk assessments, and the assumptions that are in those risk assessments are clearly laid out, if we are using a safety factor default of 100 in the absence of other information. We don't call it zero risk usually, we call it no appreciable risk, and I am talking here only about compounds which have a threshold. And the reason we call it no appreciable risk is because of the two extrapolation factors we talked about, one to extrapolate from experimental animals to humans, and one to allow for human variability.

423. And we are really talking about two different thresholds. The first threshold is the threshold in a dose-response curve, and really we have been talking about that largely today, that is when we talk about thresholds, that somewhere on the dose-response curve we reach a low dose and there is no response below that dose. But the second threshold is a population threshold, that within a population there is a variability in sensitivity, and that second threshold is the one that makes toxicologists and risk assessors reluctant to say zero risk, because we cannot say with absolute certainty, within a population of 6 billion human beings at the present, that there is not somebody somewhere under a given set of particular circumstances that might not be ultra-sensitive, so we hedge our bets if you like and say no appreciable risk. We are protecting a very very large percentile if not the entire population. I would stress, however, this does not mean to say we are not protecting certain sections of the population such as the young or the elderly, because they are definable groups and the risk assessment takes account, to the extent it can, of such subgroups within the population. We can discuss how we do that, I assume later today or tomorrow, but I am talking about a rare sensitive individual, not the population.

Chairman

424. OK. We also have related questions on the terms such as additive risk, additional risk, aggregate risk and cumulative risk. So would you explain further the differences.

Dr. Boobis

425. Additive risk. Could we maybe have those terms – OK. Aggregate risk and cumulative risk have come to mean something by definitions that were devised by the US. They defined what is meant by aggregate and cumulative risk, it is not an intuitive meaning, it is not a meaning that would automatically be understood from the words themselves, so I must stress that. So what we mean by

aggregate risk is, simply by convention, a lot of people use the term in that way, the same for cumulative risk, so that is just to clarify that. Aggregate risk in the sense that it has been defined under the Food Quality Protection Act, where this came from, is the risk from all sources of exposure to the same substance. We were talking earlier about, if we think of just oestradiol, all the different possible sources of exposure to oestradiol; if we were doing an aggregate risk assessment, we would add up all those sources together. A cumulative risk is thinking about substances which might act on the same target, so, in the case of hormones, all possible oestrogenic substances acting on the oestrogen receptor, we would have to think about exposure to all of those compounds by all different routes, and find some way of combining them. You would not just add up the amounts, because a phyto-oestrogen is going to be a lot less potent than oestradiol; diethylstilbestrol is more potent than oestradiol, so you have to normalize them for potency, which is a technical issue in respect of conducting a cumulative risk assessment. Additive risk is additional risk or risks over and above the background level of risks that already exists.

Chairman

426. So all these terms are not necessarily limited to the problems arising from the long latency period.

Dr. Boobis

427. No, they don't relate to it at all.

Chairman

428. OK, thank you.

Ms Orozco

429. Just one question. Aggregate risks – that was for Dr. Boobis.

Chairman

430. OK, we will continue to the next question and then come back to this question again. Our next question is: what are the components of a qualitative risk assessment compared with a quantitative risk assessment? Could you please clarify whether in your view the four steps of risk assessment as defined by Codex and JECFA are not applicable for qualitative risk assessment? Maybe this question could be addressed particularly to Dr. Cogliano. The EC indicated that it has carried out a qualitative dose-response assessment. We would appreciate it if the experts could provide their views about this argument, and probably the EC may also want to respond to this particular part of the question.

Dr. Cogliano

431. I would say qualitative risk assessment could be described as what IARC does when we come up with a determination that an agent is carcinogenic to humans or probably not carcinogenic to humans. It's simply the statement that a hazard does exist, without trying to further characterize that hazard as to dose level or duration of exposure of susceptible populations. This qualitative risk assessment can be a more quantitative risk assessment that could include developing dose-response relationships, establishing levels where you don't see adverse health effects, measuring exposure and comparing the exposure to the dose-response curve. So I would say, any time you are starting to get into dose-response curves and into exposure levels, you are getting into the quantitative risk

assessment; the qualitative risk assessment is just the establishment of whether a hazard exists, whether something causes cancer.

Chairman

432. You have a question?

Mr. Ehlers

433. Well actually, and I thank you for that answer, it goes on to the last part of our question. It would seem then that to say that a qualitative risk assessment, if it is qualitative, then a dose response is a contradiction, because a dose response requires quantitative, and that is why this part of the question was put in. Can you carry out a qualitative dose-response assessment if the dose is quantitative by nature? That is what we are trying to get at.

Dr. Cogliano

434. When IARC does its qualitative evaluations that end up in simply a statement that an agent is carcinogenic or possibly carcinogenic, or probably not carcinogenic, it does look at dose-response relationships because, for example in an epidemiological study or an animal study, if high levels of exposure give you higher levels of risk, that increases your confidence that you do have a carcinogen. If you had a dose-response curve that went up and down, you are not sure what you have. And so we do look at dose-response relationships. What distinguishes qualitative from quantitative risk assessment is how the conclusion is expressed. IARC expresses the conclusion by saying this agent is carcinogenic to humans or this agent is probably carcinogenic to humans, but we don't get into if it's a dose-response relationship that's linear, that there's a safe dose; that's part of the quantitative risk assessment later. So I think I would refine my first answer by saying that the difference between qualitative and quantitative is how you express your conclusions, and if your conclusions have any element of a safe dose, dose-response curve, susceptible populations, then I think you have gotten into a more quantitative assessment.

Chairman

435. So the same requirements and steps and components should be applied to the qualitative risk assessment even though their conclusion may be made in the form of a qualitative decision rather than quantifying?

Dr. Cogliano

436. I would express it this way. The qualitative risk assessment is the first of the four steps, it's the hazard identification phase. When IARC says this agent is carcinogenic to humans, we have identified a hazard. If IARC says this agent is probably not carcinogenic to humans, we have made a hazard statement that this agent probably is not a hazard, at least for cancer.

Chairman

437. Do you mean that when it comes to a qualitative assessment, stopping at the first step of the four steps could satisfy the requirements of risk assessment? I will give the floor to Dr. Boobis and then ...

Dr. Cogliano

438. I think there are cases where calling something a carcinogenic hazard has led an agency to make a decision just on the qualitative element alone. But I think many agencies still prefer to see a quantitative risk assessment that they will then carry out, based on the exposures in their country, to determine what to do. The reason IARC does the qualitative assessment only is that we really don't have the resources or the expertise to identify all the types of exposures in every country, and there does seem to be a need for an authoritative statement about what is carcinogenic and what we don't feel right now is carcinogenic. But then the next step is for national agencies or local agencies to look at their local exposure situation and compare it with a dose-response relationship or safe dose and make a determination about whether some action should or should not be taken.

Chairman

439. If we follow your views, then there would be no need to get into the exposure assessment by way of doing qualitative or quantitative dose-response assessment.

Dr. Cogliano

440. In some cases no. I would say for example cigarette smoking; I am not aware of any dose-response assessment that says your risk per cigarette you smoke is X. I think the totality of the evidence about smoking, that it causes, I think, 16 different types of cancer in the most recent IARC monograph, and just the consistency of positive results everywhere, I think is enough to have caused action to be taken. But smoking obviously is a very extreme case about having a lot data and a case where qualitative assessment is in itself sufficient to take an action.

Chairman

441. Thank you. Dr. Boobis and Dr. Tritscher.

Dr. Boobis

442. Well, I think that it does depend upon why the risk assessment is being conducted and what the risk manager requested, and in the case of a veterinary drug residue, one is seeking to determine whether residues at the level that occur in the diet are considered to be without appreciable harm or risk. And if a mechanistic consideration led to the conclusion that the hazard was such that the dose response was going to be linear, there is no threshold as we discussed just before, then it might be that one would stop the risk assessment at that point. But that would be an unusual circumstance, and in most circumstances one would want to understand the relationship between the hazard and the level of exposure that was occurring. For that reason one would progress at least to a semi-quantitative evaluation of the exposure and risk, rather than just stopping at a simple identification of hazard.

Chairman

443. Dr. Guttenplan.

Dr. Guttenplan

444. Yes. The comment was made, if you have a dose-response curve for an animal, you have a quantitative dose, why isn't that a quantitative risk assessment. Usually when you are testing a carcinogen in animals, you will test in both sexes at several doses and often in several species, and you will get different dose responses in each one of those. So just having a number for a particular animal species is not enough to produce a quantitative risk assessment.

Chairman

445. We have ten minutes before 6 o'clock so I think the Panel has – OK sure.

Ms Orozco

446. Sorry, I go back to something that was being mentioned, the aggregate risk. If you talk about evaluating aggregate risk, what that does is to modify the scope of the risk assessment, if I understand you well?

Dr. Boobis

447. It does indeed, because one of the big questions that has to be asked is how widely do you cast the net for all exposures? Do you include therapeutic application of the same drug used in deliberate administration to patients? Whose responsibility is it to take account of all the different sources of exposure? And these are very difficult questions, and on the international scene are particularly problematical because the totality of exposure will vary with the circumstances of the region, and that is one of the reasons that it has been very difficult up till now to conduct aggregate risk assessments globally. And I would add we are still struggling with this, we have not answered these questions yet, we have not reached solutions yet.

Chairman

448. EC.

European Communities

449. Gentlemen, I would not intervene, since you say the EC, that we have carried out a quantitative dose-response assessment. And I would request the scientists tonight that they have a look at our risk assessment and we can take up the subject tomorrow. We said we have carried out a dose response, in particular for the children, and I would request the scientists to have a look at our 1999 first risk assessment. We have done this for all the hormones, the six hormones. It is on page 36, 37 and 38 for oestradiol and there are corresponding pages for the other hormones, and then we can take up this issue tomorrow. I am not posing a question now, but I would request, because it is not true that we have carried out only a qualitative dose-response assessment. We explain we have examined the ADIs and the rest proposed by JECFA and those levels demanded by the US. We have tried to go through this dose-response quantitative assessment, in particular for children. As far as the genotoxicity of these substances, it is true we have made a qualitative dose-response assessment. But it is not true we did not try to do a quantitative risk assessment, and I give these pages for oestradiol but there are comparable pages for each of these six hormones. They are in our 1999 first risk assessment. They are in the documentation of all the experts. So please have a look tonight to see. We did not stop at the hazard identification, that's not true.

Chairman

450. Well, we are here not to make a decision, we are just getting advice from the scientific experts. I was expecting to see the representative of JECFA, Dr. Tritscher raised her flag on this question. We are wondering whether JECFA has done qualitative or quantitative assessments for these hormones at issue, and I am wondering whether JECFA agrees that the hazard identification alone equals a qualitative risk assessment.

Dr. Tritscher

451. Thank you. I had actually taken down my flag because I thought that we had clarified or had moved on, but it really addresses the last point here on the slide and we may have contributed in our response a little bit to the confusion in this context. So it is in the context of dose-response assessments, and dose-response assessment is an integral part of each risk assessment. Now this can be done qualitatively or quantitatively, and I tried to explain what we mean with that. In a qualitative sense, a dose-response assessment is simply determination of a no effect level. One looks at all the measured effects, identifies the dose where one sees an adverse effect, goes one step lower, the next dose lower is the no effect level. The outcome is a number, in that sense it is quantitative, that may be the confusion, but it is not doing a complete quantitative mathematical dose-response analysis, taking all the points of the dose-response curves into account. This is what we meant with the quantitative dose-response assessment. But even a derivation of a no-effect level and derivation of an ADI considers dose-response assessment, but not in a mathematical quantitative modelling way. Sorry if that raised any confusion in that context. Regarding the six hormones, JECFA did identify the no-effect levels and derived an ADI, so in the terminology, the way I introduced it, which may be a little bit misleading, this would be a qualitative dose-response assessment.

Chairman

452. Am I right to understand your comment as saying that even in the qualitative assessment you have gone through all these four steps of risk assessment?

Dr. Tritscher

453. Yes; that is the short answer. Hazard identification is not a risk assessment, a risk assessment comprises the four steps, and one can simplify it, the hazard identification and hazard characterization steps are often done together, or can be done together. This is the toxicological assessment, again, the left arm; the right arm is the exposure assessment. The integration of the outcome of these two assessments is the actual risk characterization step and yes, JECFA has done this.

Chairman

454. Thank you. Dr. Boisseau.

Dr. Boisseau

455. Please excuse me, Mr. Chairman, but I had raised my flag following the Panel's question on cumulative risk. In Dr. Boobis' example, the cumulative use of the same substance as an additive and as a veterinary drug theoretically poses a complex risk assessment problem. In practice, there may be no problem. I think we need to be fairly pragmatic, because whereas a growth promoter may be used repeatedly or even continuously, the same substance used for therapeutic purposes may only be used on a one-off basis. The evaluation of the safety of residues is something which, according to the ADI definition, is done on a long-term basis. In other words, supplementary ingestion of residues in connection with the one-off therapeutic administration of veterinary drugs is relatively less important in terms of exposing consumers to the residues of that substance. Furthermore, we must not forget that therapeutic application is not oblivious of public health. There is what is known as the waiting time. Consequently, the possible supplementary ingestion of a given substance administered therapeutically can often be considered negligible. Thank you.

Chairman

456. Thank you. Dr. Miyagishima.

Dr. Miyagishima

457. Thank you, Mr. Chairman. The Codex Commission as such does not conduct any risk assessment, but it has expressed its position on risk assessment, and this is found in the Codex Working Principles for Risk Analysis for Application in the Framework of Codex Alimentarius. Paragraph 20 of this document states that risk assessment should be based on all available scientific data. Risk assessment should use available quantitative information to the greatest extent possible. Risk assessment may also take into account qualitative information. Therefore I think that one could interpret this phrase as the desire of the Codex Commission that risk assessors use as much quantitative information as possible, whether it is in the framework of what can be seen as a qualitative risk assessment or quantitative risk assessment. Thank you.

Chairman

458. May I give the floor to Dr. Guttenplan before I give the floor to EC.

Dr. Guttenplan

459. The term cumulative risk assessment has come up, and one way that could be interpreted is the accrual of damage or mutations; if one is talking about a genotoxic substance over time. One can estimate, for instance, for certain number of years smoked you will increase your risk of lung cancer by a certain amount, or for a certain number of years of taking oestrogen replacement therapy you will increase the risk of breast cancer by a certain amount. So this is an example of a cumulative risk assessment. The longer you are exposed the greater your risk.

Chairman

460. EC has the floor.

European Communities

461. Chairman, just a quick clarification and a question to JECFA. When you identify a substance as being directly genotoxic, do you go on in your risk assessment or you stop at hazard identification? Thank you.

Chairman

462. Dr. Tritscher.

Dr. Tritscher

463. It depends, it is very difficult, again, to answer very generally on these questions, it depends very much on the mechanism, again, as was explained in detail further. With respect to oestradiol, since this was the example used in this context, and I have to correct a statement that was made earlier by the EC, JECFA stated in the report of the fifty-second meeting that the Committee, JECFA in that case, concluded that oestradiol has genotoxic potential – it is worded that way on purpose, because of the scientific uncertainty that was alluded to earlier by the experts, and I am not in a position to comment on the content there. And in that case, the risk assessment was taken further in the sense that all other information is being looked at, in particular with compounds that have a genotoxic potential. One has to, of course, as a next step look if there are cancer bioassays, does the chemical cause cancer in animal studies, in the long-term studies or not. So it is the totality of the information that has to be taken into consideration before drawing any final conclusions.

Chairman

464. EC.

European Communities

465. Sorry, I did it on purpose not to ask specifically about oestradiol, because the views of JECFA are known as genotoxic potential on this one. If you without uncertainty identify a substance as being directly genotoxic, do you then go on?

Dr. Tritscher

466. Yes, again, the answer is exactly the same. One has to take the totality of the information into account.

European Communities

467. Gentlemen, the question is if you follow the four steps if the substance – we are not talking now for this question for oestradiol – in general, if you come to the conclusion, and we are not talking about uncertainty, if you come to the definite conclusion that a substance is genotoxic, would you still go on doing the four steps?

Dr. Tritscher

468. I would say yes. It depends on what level of detail you go into. But now I have to, apologies for the time, but I have to explain a little bit longer, because its very different if we are talking about compounds that are added to foods for a specific purpose, or if we talk about unintentional and potentially unavoidable contaminants, that is a very different story. But traditionally in the food safety assessment area for compounds that have been added intentionally to food, veterinary drug residues, pesticides, what have you, if there is in *in vitro*, *in vivo* studies a clear-cut conclusion that the compounds are genotoxic, and traditionally no formal risk assessment was performed in a sense, not quantitating it and so forth, but the recommendation, and I guess that is what you want to hear now, that's what you are alluding to, is invoking the so-called ALARA principle, meaning that exposure to compounds that are unwanted in food should be reduced to as low as reasonably achievable. Again, one has to differentiate between unintentional compounds and intentional compounds, to say very briefly, and it is up to the risk management to make decisions on the regulatory level what to do to reduce exposure. For example, with compounds that are added, like veterinary drugs, one can make different legislative ruling than for example for contaminants.

469. Now going back to the contaminants, JECFA as well as EFSA, the European Food Safety Authority, and then together in a joint EFSA/WHO effort, is trying to go a step further to get away from this ALARA principle, to give more advice to the risk managers for contaminants in food that have genotoxic and carcinogenic properties, which includes compounds where you cannot necessarily make the link; there are genotoxic properties, carcinogenic properties, not necessarily linking that the carcinogenic mechanism, the carcinogenicity has to be provoked by genotoxic mechanisms. In order to give better directions to the risk managers as to which compounds are really of public health concern – so where to put your efforts, for management measures, for public health protection, the concept of the margin of exposure has been now formalized. I want to say it is not a new concept, but formalizing it, which compares certain effect levels for model studies with the estimated human exposure, and the larger the difference between those two, the lower the public health concern. By formalizing this approach, this allows comparison between different compounds, and gives some indication which are of more concern to health than other compounds. But having said this, I have to

emphasize again this is a concept that JECFA applied or developed a formalized approach now, and it is applied only to contaminants. Thank you.

Chairman

470. Even if in seven minutes it's already 6 o'clock, I think this is a rather important issue, so I will continue until we complete discussion on this particular issue this evening. I am wondering whether interpreters are available until that time.

Interpreter

471. Could you tell me how long you might expect to last, how much longer you would like us to be here? I will have to check. I think that is alright but I will check with my superior. Thank you.

Chairman

472. May I request each one of the experts to be as brief as possible in his or her response to this question. Dr. Boobis.

Dr. Boobis

473. Briefly, just from an independent scientific perspective, regardless of whether I participate in JECFA or not, if I was talking about a veterinary drug which was generating a residue and were evaluating that compound and it was shown to be a DNA reactive mutagen which was expressed *in vivo*, I would consider it unnecessary to proceed with the risk assessment, with a proviso that for any reason the risk manager did not ask for some scenario evaluation. For example, it might be that there was a particular essentiality for that compound and the risk manager might say well, what is the margin of safety, along the lines Dr. Tritscher has just outlined, it would be possible to conduct a risk assessment on that basis.

Chairman

474. Thank you. I saw many flags raised a few minutes ago. EC.

European Communities

475. Gentlemen, we are grateful for the intervention of Dr. Boobis, because on the basis of what we have been hearing from the representative of JECFA, then an exposure assessment in that situation, that means where you had a genotoxic substance, defined and uncontested, you only need to count how many people will die definitely, and the question is why you are supposed to do it, because this is the question, why you are going to go along with the risk assessment if you know that the substance is genotoxic? And by the way, I would like to ask, how are you going to do it since you don't know if there is no threshold there? So I appreciate the intervention, because it clarified the situation.

Chairman

476. Thank you. Dr. Boobis.

Dr. Boobis

477. I regret that I have been misrepresented, Chairman. I have chosen my words with extreme care – I would like to repeat, I said a DNA reactive mutagen. I would also like to point out, although

we have not got into this yet, when JECFA evaluated the specific compound in question – and what my answer was was a general answer – the specifics are that they did not conclude that that compound was a DNA reactive mutagen, which is the reason why JECFA was able to proceed with this risk assessment, it felt it was appropriate to do so. These are different scenarios. As I stressed before, and I do again, it depends entirely upon the conclusions that an evaluation of the data lead to as to how you proceed.

Chairman

478. Thank you. Dr. Boisseau, and I will conclude

Dr. Boisseau

479. Yes, thank you Mr. Chairman. I simply want to mention, since we are speaking of general principles, that it is obvious that if a product has been shown to be mutagenic following a series of tests, it will be mutagenic for the target animal. But we are not talking about a target animal, we are talking about the consumer, so that the risk remains for the consumer to the extent that the mutagenic product is present as a residue. Imagine a parent substance that is definitively mutagenic but that is completely metabolized: I have in mind carbodox, for example. The substance, which is toxic as such, may not ultimately generate toxic residues in the foodstuff. So the evaluation must always be comprehensive, and indeed, stopping an evaluation as soon as a hazard has been detected, without trying to evaluate the possible risk for public health, is a procedural shortcut that could lead to an erroneous assessment of the risks without necessarily providing a comprehensive and reasoned view of the case as a whole.

Chairman

480. Thank you. We do have some more questions that, I am sure, will be asked by the parties, because some them have already made comments in relation to conflicting evidence on the table and so on. So I would rather stop our discussions this afternoon here and see you tomorrow morning at 10 o'clock in this room. But before I adjourn the meeting – excuse me, there was a request from my colleague in the Panel to go on. Instead of getting into the question and answer session again, on the remaining questions, I just want to put the questions verbally so that you can consider these questions for the discussion tomorrow morning in responding to the questions posed by the parties.

481. Our question was on the weight of evidence approach, which was, to my knowledge, used by Dr. Boobis, and the remaining two questions are: please comment on the EC statement in its comments on question 19, where it states that it has a standing request to review the hormones at issue. The last question is about Codex and JECFA. In response to question 3, Codex makes reference to ongoing work regarding risk analysis principles applied by the Codex Committee on Residues of Veterinary Drugs in Food and risk-assessment policy for the setting of MRLs in food. Do you expect major changes to Codex/JECFA work in this area once these documents are adopted? These are the remaining questions for your consideration at tomorrow morning's session.

482. Thank you for your cooperation, and I particularly appreciate the patience and cooperation of the interpreters for staying with us until this time and I hope you will have a good evening and see you tomorrow morning at 10 o'clock sharp in this room.

28 September 2006, morning

Chairman

483. Good morning. I hope you all had a good sleep last night and, for those who have travelled a long way from another continent, recovered from the jetlag, I hope.

484. This morning we are going to continue the remaining questions on area 2. As you may recall, before we adjourned the meeting yesterday afternoon, the Panel read out three questions, the question, Nos. 18 and 23 and 24, which you might have noticed on the screen, but we believe that 24 has already been answered by JECFA representative, so I hope we can start with the experts' replies to the Panel's questions 18 and 24.

485. For your reference I will read out the questions once again: could you please explain what the weight of evidence approach is? And the other one is: please comment on the EC statement in its comments on question 19 where it states that it has a standing request to review the hormones at issue. These are two remaining questions of the Panel on which we expect the replies from the experts at the beginning of this morning's session. And then, as I mentioned in my opening statement yesterday morning, the Panel will invite parties to pose their own questions to the experts on the area 2 items. And on area 3, the Panel has the intention to let the parties go first with their own questions and then the Panel will follow up the questions already posed by the parties. And I would like to remind the delegations that we have a time-limit to finish our business until the end of this session. And also I would like the delegations to know that one of the JECFA representatives, Dr. Tritscher, has a prior engagement this afternoon, so she has to leave after the lunch break. So we have to finish our discussions on the remaining questions under area 2 and, if possible, all the questions under area 3, that is scientific evidence, and there are many JECFA-related issues even under area 3. So I hope we can conclude our discussions on area 2 and area 3 this morning so that we can move into the remaining areas, that is EC's risk assessment and others. So, all in all, time is very constrained, so I hope the parties will be very strict in selecting the questions of their own, so that they can economize the time given during the remaining meeting today. Before Dr. Tritscher leaves this afternoon, parties are requested to pose questions on JECFA-related issues this morning, even if that falls into the category under area 3, that is scientific evidence. I am not sure whether I was quite clear to the delegations.

486. OK, with that understanding may I ask the experts to respond to the Panel's questions on Nos. 18 and 23. Dr. Boobis.

Dr. Boobis

487. Mr. Chairman, I would like to address the issue of weight of evidence. The weight of evidence is the evaluation of the available information about a particular toxicological endpoint, taking into account factors such as the adequacy and number of available studies and the consistency of results across studies. It is not an issue of seeking to weight one person's opinion against another. It is a specific situation where one is faced with a large body of information on a particular endpoint, and we can talk about, for example, genotoxicity. Where there are multiple tests of genotoxicity, and the results of those tests are not entirely consistent, a weight of evidence approach requires an examination of the quality of each study individually – because sometimes the studies will not all be done to the same standards – and the consistency across those studies, and then eventually an evaluation of what is the totality of the evidence telling us about that endpoint. Thank you.

Chairman

488. Thank you. Any others – Dr. Boisseau.

Dr. Boisseau

489. Thank you, Mr. Chairman. I would like to support what has just been said by Dr. Boobis concerning the genotoxicity and mutagenicity tests. In fact, these tests currently pose a double problem, I think. Over the past twenty years, the number of such tests has increased considerably, with the inevitable result that since we are using a greater number of tests to study a substance, the chances of our ending up with a positive result obviously increase accordingly. The second problem is that these tests, which have flourished over the past few years, have not always been validated according to internationally accepted criteria – so that whereas fifteen years ago when a committee of experts considered the results of a series of what was usually four tests, two *in vitro* and two *in vivo*, where there were one or two positive tests it was not too difficult to declare the substance genotoxic or mutagenic, today we always have one or two positive tests and two or three dubious tests out of a total of fifteen; and when the tests used have not necessarily all been validated, it is easy to understand that the willingness of a committee of experts to declare the substance genotoxic or mutagenic is not very strong. Thank you Mr. Chairman.

Chairman

490. If there are no other additional comments, then shall I move into the next – OK, then I will open the floor for EC.

European Communities

491. Thank you. Without wishing to prolong the debate, I would like to ask the scientists which have responded and also the other scientists which have not taken the floor: the United States 2002 National Carcinogenesis Reports have classified oestrogen and oestradiol as capable of causing direct and indirect damage, cancer. This is part of the file we have submitted to the Panel and you must have it. Is it clear? The question then is: in your conception of the weight of the evidence approach, where would you place this United States National Carcinogenesis Report? Why is it not part of the weight of the evidence?

Chairman

492. Dr. Boobis.

Dr. Boobis

493. The report on carcinogenicity of the United States is the consequence and evaluation of the data, it is a conclusion. The weight of evidence approach requires a de novo evaluation of the data, so you don't use somebody else's conclusion in a weight of evidence approach. You may ask the question why does one reach a different conclusion, that is a perfectly justifiable question, but it is not appropriate to take other people's conclusions in a weight of evidence evaluation of the data.

Chairman

494. US and then EC.

United States

495. Thank you, Mr. Chairman. I would like to follow up on Dr. Boobis's comments and on the EC citation to the 2002 US report on carcinogens, and actually this is a question to Dr. Boobis with a short lead in. The EC has cited this report as evidence that steroidal oestrogens *per se* are known to be human carcinogens, and as you might be aware if you have looked at this report, the conclusions

rely heavily on an evaluation conducted by IARC in 1999 entitled Post-Menopausal Oestrogen Therapy. Dr. Boobis, if you are familiar with the US report on carcinogens and these IARC monographs, can you comment on the relevance of these reports to the specific risk alleged by the EC, which is that posed by oestradiol 17 β residues in beef and beef products?

Chairman

496. Dr. Boobis.

Dr. Boobis

497. I am certainly familiar with the IARC evaluation and familiar to some extent with the RC. As I understand it, the conclusion was that oestradiol-17β was a likely human carcinogen; but neither of those reports, as I understand it, said that genotoxicity was the mode of action. And, based both on the evidence of other bodies and also on its own primary evaluation of the epidemiology – because at that meeting there were distinguished international epidemiologists present who did their own evaluation of the world's literature on the possibility of a risk of cancer from exposure of humans to oestradiol-17β – JECFA accepted at that time that was a risk. But, and it is a very big but, the conclusion was that this was not associated with genotoxicity. And critical to the JECFA evaluation was the relative level of exposure, and the conclusions of JECFA were based on an evaluation of the exposure that was likely to occur from the use of the hormones in beef-producing animals.

Chairman

498. Thank you. EC.

European Communities

499. Thank you, Chair. A simple question, going back to the weight of evidence and the explanation given by Professor Boobis. I would just like to know whether you mean to say that the weight of evidence approach involves interpretation of data of the kind you have explained in your reply to question 52. Thank you.

Chairman

500. Dr. Boobis. Is Dr. Boobis ready to respond?

Dr. Boobis

501. In fact, the IPCS report to which I refer did use a weight of evidence strategy. I was using weight of evidence in a narrower sense in my earlier response in that we were very much focussed – and this is common practice when one is dealing with multiple studies on the same endpoints, or related endpoints, one has to have some process to determine what is the consensus picture of that data set. This is not a question of what people think and minority opinions, it is a question of looking at the data, and we had an expert genotoxicity person with us at that meeting to help us to evaluate the quality of the studies and the likelihood of outcome. Now when one looks at genotoxicity testing, some tests are more prone to artifactual results than others. So an Ames test, the bacterial test for mutagenicity, is generally a very reliable indicator of DNA damage, because there are few ways in which one can generate an artifact if the test is done to a reasonable standard. If one looks at some other tests, toxicity and other methods of interfering with a cell can influence the endpoint, so it is very important that one looks under the conditions of the protocol of the study as to the reliance that one is placing on the endpoint of that study. When one looks at 100 studies of genotoxicity, for most compounds one can find the odd positive, even for a genuinely negative substance. And so that is

what I mean by the weight of evidence. If you have 99 negative studies all done well, one study done badly which gives a positive, what is the weight of evidence? The compound is negative. I am not arguing this is the case with oestradiol-17β, is was not quite as clear-cut, but using a weight of evidence approach, the committee was able to reach a conclusion as to what the genotoxicity was telling us, and that was the case for many other organizations that have looked at the body of evidence available for this compound's genotoxicity. There is an element of interpretation of the quality of the study, I accept, but that is why you have experts on the evaluation committee.

Chairman

502. EC.

European Communities

503. So Dr. Boobis and also the other scientists, do you accept that different groups of scientists can view the same set of data and reach different conclusions to that question?

Chairman

504. Dr. Boobis.

Dr. Boobis

505. The simple answer is yes, one can always get different interpretations with the same dataset, but some datasets are more likely to give a consistent answer than others for most people, if that makes sense. So the example I gave earlier of 99 good studies giving a negative, or let's put it the other way around, 99 good studies giving a positive and one bad study giving a negative, one would hope that the vast majority of people looking at that dataset would reach the same conclusion. It is just possible that somebody would say that the negative study is the one we should put the weight on.

Chairman

506. Let me give the floor to Dr. Guttenplan and Dr. Boisseau first.

Dr. Guttenplan

507. Yes, I guess I want to answer some of the questions. I think it is probably fair to say that most of the agencies that look at or have looked at these compounds or other compounds use a weight-of-evidence approach. I think that is true of the National Toxicology Program Report on Carcinogens, it is certainly true of the IARC monographs. It means that you get a lot of experts together and they look at the positive and the negative studies, they consider multiple interpretations, they try to weigh which studies should contribute most to the evaluation and come up with a reasonable judgement. Also, as Dr. Boobis said, it is possible for different groups of experts to come to different opinions. That is why we invite groups of experts, so that we are not too dependent on any one person's opinion. And in most cases when the IARC monographs programme looks at data, they do have a consensus, although there are cases where the dataset is sufficiently mixed that there is a close vote. So there are some cases where the overall signal about whether something is carcinogenic is an issue. I don't think that is the case with steroidal oestrogens, I think many bodies have said that steroidal oestrogens are carcinogenic. I think that the next level down of questions is: How is it carcinogenic? Is it carcinogenic through a hormonal mechanism, through a genotoxic mechanism, only one of them, possibly a mixture of both? And I think that there is some uncertainty and there is some difference of opinion among the experts. So in that case it is possible for different groups of people to reach different evaluations.

Chairman

508. Thank you. Dr. Boisseau.

Dr. Boisseau

509. Thank you, Mr. Chairman. I would go along with what was just said. The fact is that expert committees are currently issuing different opinions in the area of genotoxicity, perhaps because they are focusing more on the results. I am convinced that if we brought together competent and independent experts and if they began by objectively evaluating the validity of the methods, there would be far fewer problems with the results that those methods produce. I do not think that we place enough emphasis on the validity of the methods. Secondly, to favour consensus, it is important to know what these short-term mutagenicity or toxicity tests can produce and what they cannot produce in order to avoid erroneous interpretations depending on the results obtained. Clearly these techniques are used with large quantities of the substance that have nothing to do with residue content. This is particularly true of *in vitro* methods: they are conducted in conditions which do not reflect the fate of a substance in an organism, determined by pharmacokinetics and the metabolism – they are merely screening tests, and nothing more. They cannot, under any circumstances, lead to a determination of dose effects, and at best, they can only provide information on the mechanisms of action. Thus, if the experts focus on the validity of the methods, on what these methods can produce and what they cannot produce, I am convinced that there would be much more consensus on the interpretation of the results of the methods. Thank you.

Chairman

510. I have a procedural question. What if there are conflicting views, half and half, or almost half and half, among the experts participating in the JECFA Committee? What is the decision-making process in that case? Do they still make conclusions on the issues that do not provide any sufficient scientific evidence, or avoid making decisions and refer it to the next committee or to a later stage? Dr. Boobis.

Dr. Boobis

511. First of all, Chairman, this is a hypothetical question, because it has not occurred. I want to make that clear. The JECFA Committee – at least as far back as 1997 – have been able to reach an agreed position on all the questions before them. In the event that there was a disagreement, there would be two possible options – one would be not to proceed further and seek further evidence, and the other would be, as has been indicated already by the secretariat, if the majority was of one view and a minority was of another view, to issue a so-called minority opinion or minority report as well, which reflects a contrary view on the interpretation of the data. As I said earlier, this has not happened, there was unanimity. Generally what happens is that there is a discussion, there may be varying interpretations of a dataset, the experts get together over the period of a meeting and explore the various possibilities, bringing new information, or new insights and reach a common position, and that has worked generally very successfully in the evaluation of the compounds over the last 10 years I have been involved in JECFA. Thank you.

Chairman

512. Are all these decisions made by consensus, or sometimes by voting?

Dr. Boobis

513. At JECFA the decisions have always been made by consensus, to my knowledge no vote has been necessary.

Chairman

514. Dr. Tritscher.

Dr. Tritscher

515. Thank you. I have to explain a little bit what I did not do in the beginning, what the role of JECFA is within the WHO Constitution. JECFA is an Expert Committee, and expert committees are the highest level scientific expert groups that exist within the WHO Constitution, and there are very strict rules for scientific groups. And as I said, an expert committee is the highest-level committee with very stringent rules with respect also to the selection of the experts and so forth. With regard to decision-making, it is the basic documents of the WHO which lay out the rules for expert committees, which are convened to develop a recommendation to the Director General for his or her decision. It is made very clear that scientific decisions are not subject to vote, that is very clear. And as Professor Boobis said, your question is indeed a hypothetical one because the whole purpose of an international expert committee is to reach a conclusion. If theoretically there would be a situation where you have a 50/50, 60/40 or very close decision, and then it is in the discretion of the Chairman on how to proceed. If it appears that no consensus opinion will be reached, then that subject would not be concluded on. If there is a minority, then there are also very clear rules, and there is the option that if it is not possible to reach consensus, a minority opinion can be expressed, and has to be expressed, if there is no consensus. And again, this minority opinion is published in the report, with the names of the experts having this minority opinion and a clear description of their rationale and their opinions. Thank you.

Chairman

516. Dr. Wennberg.

Dr. Wennberg

517. Thank you, Mr. Chairman. Yes, as I was explaining yesterday, the existence of scientific committees is also laid down in the basic text of the Food and Agricultural Organization of the United Nations, and as Dr. Tritscher explained, the same rules apply to the experts which participate in expert committees called by FAO to help the international scientific committees to elaborate on scientific issues. And may I also say that as far as the expertise is concerned, there is a transparent procedure in how these experts are called upon, are selected, are put on rosters which are agreed by the Director-General of FAO and by the member countries from where these experts are coming, and the experts have to sign a declaration of interests for every meeting in which they participate, and these declarations of interests are filed by the Organization. Thank you.

Chairman

518. Thank you. EC.

European Communities

519. Chairman, can I make a short statement instead of a question, or it is both. A clarification for Dr. Boobis. In the United States 2002 carcinogenesis report, is it not true that they examined and

declared oestradiol as a direct and indirect genotoxic substance? They have also said, and I can read, veterinary use of oestradiol estrogens to promote growth and treat illness of animals can increase oestrogens in tissues of food-producing animals to above their normal levels. This is in the report. They didn't make just a general finding, they have linked it to the residues from meat of animals treated with hormones for growth promotion, it is written in the text. And later on we come to the more precise question of the growth response. Thank you.

Chairman

520. US.

United States

521. Thank you, Mr. Chairman. I think you know that the issue that the EC has raised is one that we can discuss on Monday of next week when we discuss these issues. But I would note that the statement made by the EC is nowhere linked, in that report, to the carcinogenic effect that the EC seems to be alluding to. So just as a point of clarification, and perhaps any of the experts who have read the report would like to speak to that issue.

Chairman

522. OK. Question 23 regarding the EC statement that it has a standing request to review the hormones at issue has not been answered by the experts or the JECFA representatives. Dr. Miyagishima.

Dr. Miyagishima

523. Thank you, Mr. Chairman. Yesterday I explained briefly how the Codex Committee on Residues of Veterinary Drugs in Foods operates, but please let me reiterate what I explained yesterday a little bit, and answer the question posed. CCRVDF uses the so-called priority list as a means of communication with JECFA. Prior to each meeting of CCRVDF, the Codex Secretariat circulates or distributes a circular letter to all Codex members and observers, and this circular letter invites any nominations of compounds for evaluation or re-evaluation. The comments or proposals received in reply to the circular letter are usually considered by an ad hoc working group that meets the day prior to the beginning of the CCRVDF session. The discussion and conclusions of the ad hoc working group are presented to the plenary session of CCRVDF where the final decision takes place as to what compounds should be included in the priority list and then communicated to JECFA.

524. Now, with regard to the five substances for which the Codex established MRLs, that is, oestradiol-17β, progesterone, testosterone, trenbolone acetate and zeranol, the only reference found in the reports of CCRVDF is the intervention made by the European Commission – which was an observer at that time, participating in CCRVDF – on behalf of the European Community, at the eleventh session in 1998. The European Community requested that the re-evaluation of these five substances that was being scheduled in 1999 be deferred to a later session of JECFA, in view of substantial studies that were being prepared by the European Union at that point of time. Since 1999, CCRVDF has met five times, as I explained, at the interval of approximately 18 months. In the reports of CCRVDF, there is no record of proposals, either from the European Community or from member States of the European Community, to include these five substances in the priority list for re-evaluation by JECFA. With regard to melengestrol acetate, it was included in the priority list for recalculation of MRLs and TMDI by the fifteenth session of CCRVDF that met in 2005. However, the request did not come from the European Community, but came from an industry observer present at the meeting. These are the records found in the reports of CCRVDF, and given the fact that Codex rules or internal procedures allow for any member to go on record for any decisions taken by

CCRVDF contrary to its wish, it is unlikely, reading from the reports of CCRVDF, that a request was made from the European Community for re-evaluation or evaluation of these substances. Thank you.

Chairman

525. Thank you. Madam Orozco.

Ms Orozco

526. Thank you, Mr. Chairman. I have two follow-up questions, one to the EC, as to what they means by a standing request to review the hormones at issue, because that has been stated in some of your documents. I would like clarification as to what the actions are, or how this request has been submitted. And second, I have a follow-up question to the Codex representative as to what was the answer, and the reasons for the answer to that intervention by EC requesting postponement of the re-evaluation. Thank you.

European Communities

527. Mr. Chairman, I can be very brief on this. We have sent to the Panel Exhibit No. 63, where we have attached the exchange of letters we had with the JECFA and Codex secretariat. In the last letter, the reply of the joint secretariat, it is stated that we had been requesting JECFA to postpone the re-evaluation of 1999, which nobody has requested. It was coming from the secretariat themselves, which is a very rare procedure to apply. And we have requested them to postpone because the new data was coming. And they have replied to this letter that once the new data becomes available we will review them, and they conclude we will be happy to place again these substances on the agenda of a future meeting of JECFA. And the issue was left there. We never said after the re-evaluation don't do it, it was there on the table since we were communicating on this question since 1999. It is true we didn't put it on a priority list subsequently, but the understanding was, at least this is how I understood it, that when the new data become available, they will review that. And the truth is, when they presented the 1999 evaluation to the Codex Committee, they said we did not ask you to re-evaluate, and they didn't consider that. So I think it would be reasonable, in the light of these letters which we have exchanged, and the promise that they will be happy to place again these substances on the agenda, they would have done it. That is all, it's no more than that. Thank you.

Chairman

528. Thank you. Dr. Miyagishima.

Dr. Miyagishima

529. Thank you, Mr. Chairman. Just to complement my previous intervention by saying that the latest session of CCRVDF actually met earlier this year, and there was a circular letter, Codex circular letter 2005/43, was circulated in September 2005 to invite nominations for compounds for evaluation, with a deadline of 28 February 2006. No replies were received from any member or observer. Thank you.

European Communities

530. Excuse me. I have the question for Codex and for JECFA as to what was the answer to the intervention made by the EC observer referring to the deferral of the re-evaluation.

Dr. Miyagishima

531. The request from the European Commission made at the eleventh session of CCRVDF was duly recorded in the report of that particular session and as such it was brought to the attention of the JECFA secretariat, and that was the action taken by the Codex side.

Chairman

532. Thank you. Dr. Wennberg.

Dr. Wennberg

533. Thank you, Mr. Chairman. The JECFA secretariat and the exchange of the letters that was talked about – the reason why JECFA put the substances on the agenda of JECFA was that there was new important epidemiological data that had become available since these substances had been evaluated in 1987. The JECFA secretariat may place any substance on the agenda for re-evaluation, even though no outside request has been received. It is not permissible that the JECFA secretariat should postpone a re-evaluation of a substance when new important information has come to the attention of the secretariat – let's make that clear. The second point I would like to make is that the procedure to put substances on the agenda of JECFA, through the CCRVDF, is open to all members of Codex and even observers, as we have heard. So it's not because there is a letter responding to this request for postponing a re-evaluation that the secretariat would issue a call for data for re-evaluation of the substances when there is no explicit request from a member of Codex to do so. The procedures have been very well explained by Dr. Miyagishima and they are followed by everybody. The secretariat never received any information on the studies, the studies themselves, or the study report from the EC. Thank you.

Chairman

534. Thank you. Dr. Tritscher.

Dr. Tritscher

535. Just to add to what my colleague already said, it's really that there are three main routes or main ways for a compound to get on the agenda of JECFA; through the priorities working group in CCRVDF, but also requests from FAO and WHO member States can be brought forward directly to the JECFA secretariat with the request for evaluation or re-evaluation, with justification, data availability and this kind of information. And the third is that the JECFA secretariat can re-schedule the re-evaluation of a compound if they are made aware that there is significant new data available. What that requires usually is that these data are really made available, not just saying that there are new data, here it is, but there has to be a very clear list of what type of data, to allow, with the help of experts often, to judge if this is justified, if the data are significant enough to justify a re-evaluation. And it is not correct that this is an extremely rare procedure. Sorry, there is one other way for compounds to be nominated for evaluation; it is actually through specific FAO and WHO programmes themselves. It is commonly the case that, for example for the WHO drinking water guideline programmes, compounds are requested for evaluation through JECFA or through JMPR for pesticides. And although the main route for nomination of compounds for evaluation is through the Codex Committee, it is not correct to say on the other side that it is extremely rare; it really happens frequently. Thank you.

Chairman

536. We now invite the delegations to pose their questions. Starting with EC.

European Communities

537. Thank you, Chairman. So we move now to another area.

Chairman

538. Another area, you mean area 3, or are we still in the risk assessment techniques? Have you exhausted all your questions on item 2? Do the US and Canada have any questions on risk assessment techniques? Canada.

Canada

539. Thank you, Mr. Chair. Our questions are just clarifications on some of the answers that have been provided. First for Dr. Cogliano. You said yesterday that IARC conducts qualitative risk assessments in that it stops after identifying a hazard. You also said that it's qualitative because of the way it expresses its conclusion as possibly carcinogenic or a known carcinogen. My question is, then, can you use the qualitative conclusions of a JECFA monograph to evaluate the potential for occurrence of the hazard that is identified for given exposure scenarios? Perhaps – you are going to answer that one first then.

Chairman

540. Thank you. Dr. Cogliano.

Dr. Cogliano

541. It is true, the IARC monographs do stop with a statement that something is carcinogenic or probably not carcinogenic to humans. That can be enough, depending on the structure in which you make a decision. The monographs on different forms of tobacco were enough for WHO to conduct its framework convention on tobacco control. It does not give you dose-response information about what is happening at lower doses; it will simply tell you what are the substances for which carcinogenicity should be considered, and then different decision-making authorities will have to decide whether that evidence is sufficient for them to make a decision, or whether they do need to conduct further analysis.

Chairman

542. Thank you. Canada.

Canada

543. On its own, then, the conclusion is not useful for evaluating occurrence in a specific exposure scenario though, is that what I understand? It might lead other authorities to determine in specific circumstances whether there is a risk that that particular hazard would occur.

Dr. Cogliano

544. Yes. Other authorities would need to determine whether there is a risk. Now occurrence is a different matter. Occurrence simply means is there some exposure to the chemical through some particular pathway. The IARC monographs do attempt to identify the different types of exposures people encounter, whether it is occupational exposure, whether something is found in food, whether something is widespread in the environment; so the monographs identify occurrence, but not the

specific levels of exposure in a particular population. There are a lot of terms, like occurrence, exposure, risk and I'm trying to be precise here.

Chairman

545. Thank you. Is that all Canada?

Canada

546. I have just two more questions. Dr. Boobis, you explained the difference between deterministic approaches and probabilistic approaches to risk assessments. I wonder if you could comment further on – I think in fact you did comment on – which approach is more often used, but if you could further comment on which is the more conservative of the approaches.

Chairman

547. Dr. Boobis.

Dr. Boobis

548. In terms of the toxicological side, the hazard side, of risk assessment, the probabilistic approach has only very rarely been used. We almost always use a deterministic approach. In terms of the exposure side, the majority of risk assessments have also used deterministic approaches, although increasingly people are using probabilistic approaches. Where data have been obtained, it is quite clear that almost always the deterministic approach is more conservative than the probabilistic approach, and sometimes by orders of magnitude.

Chairman

549. Thank you. Canada.

Canada

550. A final question then, Mr. Chairman, and this would go to the representatives of the JECFA secretariat, or I guess any other expert that is familiar with the operation. In light of the suggestion by the EC in its comments that JECFA takes for granted all the unpublished data from industry, I wonder if you could describe the steps that JECFA takes to verify the quality and sufficiency of the preparatory data it receives from industry. Thank you.

Dr. Tritscher

551. Thank you. I don't understand what is meant with taking for granted, maybe that has to be explained later if I am not addressing what is actually meant with that. When compounds are put on the agenda, the JECFA secretariat publishes a call for data on the internet that goes out publicly to everybody. With compounds that are commercially produced and sold, very often important toxicological information is proprietary information and is not publicly available. This information is submitted by the company to the JECFA secretariat, and JECFA requests the complete study reports, so not the summaries or the conclusions or what have you, but the complete detailed individual reports with all the details, individual numbers, individual data, completely the whole set of information. And in addition, all the experts perform literature searches using standard techniques in order to, in addition to the non-publicly submitted information, to take into account everything that is publicly available in the public domain as relevant scientific information. The data that are submitted are scrutinized in detail by the JECFA experts, in particular with respect to quality of the study. There

are criteria with respect to good laboratory practice that are very well defined. Modern newer studies have a statement to that effect, a legal statement, quality assurance statements, statements regarding good laboratory practice in their study reports. All those studies before these methods were implemented very often do not have such official quality-assurance statements and so forth. And then it is the responsibility of the experts to scrutinize in detail the study reports, if current good laboratory practice techniques have been followed. That means characterization of the test material, appropriate analytical methodology and any kind of really basic information that is available. If this is not available, if it is concluded that a study was not conducted according to what would be called good laboratory practice; it does not necessarily discredit the study as such. Sometimes these studies can still contain important information, in particular if you talk, as was explained earlier, in the context of the weight of evidence approach. Sometimes such studies still give important information, but one would not base an evaluation on such studies. It is in the overall context of evaluating the whole database. And again, all the data that are submitted are scrutinized in detail, checked for accuracy and then summarized and described in detail. I hope this addresses the question.

Chairman

552. Canada.

Canada

553. That concludes our questions on item 2. Thank you.

Chairman

554. Thank you very much. May I now invite the EC to pose questions on item 3, scientific evidence. Please go ahead.

European Communities

555. Thank you, Chairman. I would like to come back to the issue of the most sensitive segment of the population, in particular prepubertal children, and I would like to ask Dr. Sippell, for example, whether the values which we have seen yesterday on the screen from JECFA are the values for prepubertal girls and boys which are their actual production rate, daily production rate, or whether they are based on the detection limits of the assays used for the calculation.

Chairman

556. Dr. Sippell.

Dr. Sippell

557. As far as I could see the official production rates, and it is difficult to calculate exact production rates in prepubertal children because first you have to have a true level of endogenous production, blood levels, so that you can calculate the production rate. They have been based on the, so to speak, traditional levels measured by radio immuno assays, and usually by radio immuno assays without prior extraction. We all know that the sensitivity of such procedures is not enough compared with more modern techniques, so to speak, the extractive procedures involving radio immuno assays, but even more modern molecular base techniques like recombinant cell bioassays, of oestrogen, oestradiol or oestrogen activity. And these, as I have pointed out in my answers to the Panel, are significantly below the levels previously thought, and by that the production rate now is significant lower. And this of course implies that any risk from exogenous sources, for example beef treated with hormones, treated with oestradiol-17β, is much higher.

Chairman

558. Thank you. EC.

European Communities

559. You have also made reference yesterday to the latest method in the USA to calculate the daily production rates, and you made a reference to the assay of the group of Klein which became relevant after the evaluation made by JECFA, so does this in your view put in doubt the validity of the values given in JECFA, and I am precise as to the potential risk for prepubertal children from eating meat treated with hormones for growth promotion. It's an important point to clarify in my view. Thank you.

Chairman

560. Dr. Sippell.

Dr. Sippell

561. Yes, that's indeed the case. This ultra-sensitive assay has been recently confirmed, its validity has been confirmed by another lab, you know the Klein methodology. The main author is George Chrousos, by the way, who was for many many years director of the children's section at the National Institutes of Health, and this new supersensitive assay has been confirmed by another laboratory which also is very well-known and considered to be very thorough and applying good laboratory practices, of course; that is the lab of Professor Charles Sultan in Montpellier, and coming to quite similar levels and, as I said yesterday in my introduction, many basic biological features can only be explained by the validity of these supersensitive oestradiol assays. There is no other explanation among scientists, among paediatric endocrinologists, than very very low levels, significantly higher levels of secretion in prepubertal girls, significantly higher than in prepubertal boys. Therefore there is no doubt, as I told yesterday already, there is no doubt among the scientists, also in the United States and Canada, that this is really the case, and this supersensitive assay is not being put into doubt really by the experts I have been speaking to. Therefore, there really is concern that the exogenous load from, for instance, oestradiol-17β, might be significant.

Chairman

562. I will give the floor to the US and then back to EC.

United States

563. Thank you, Mr. Chairman. Just as a point of clarification, to the best of our knowledge the Klein assay has not been used subsequent to its 1994 publication for regulatory purposes. But beside that point, I think there are two important questions here, one of which I would like to pose to the experts generally, which is: what does it mean when an assay is validated? And I think the follow-up to that is an appropriate question for Dr. Boobis, which is: given the considerable debate in these proceedings regarding blood levels of oestradiol in prepubertal children, and given the EC's heavy reliance on the Klein assay which purportedly shows lower circulating levels of oestrogen, I was wondering if in Dr. Boobis's opinion the Klein assay indeed establishes that circulating oestrogen levels in prepubertal children are lower than previous reported, and whether that assay has indeed been validated by the evidence that is on the record? So a two-part question, one to all the experts – what does it mean to validate an assay? and then secondly – has the Klein assay indeed been validated? – to Dr. Boobis.

Chairman

564. Is any expert prepared to answer the first part of the question? Dr. Guttenplan, please.

Dr. Guttenplan

565. If an assay has been confirmed independently in a number of laboratories, I would consider that validated.

Chairman

566. Dr. Boobis.

Dr. Boobis

567. I am not an expert on residues, and there are people here who can speak on this better than me, but as I understand it, in residue analysis the process required for assay validation to measure and analyse biological samples for regulatory purposes is fairly well defined and consists of a number of steps, such as ruggedness, precision, sensitivity, reproducibility, transferability, availability of standards, etc. etc. There is a procedure which the chemical societies have agreed internationally, that before an assay can be described as validated, as opposed to fit for purpose, these are different things, that for validation it has to undergo this procedure which has been recognized as a systematic analysis of the different performance characteristics of the assay.

Chairman

568. Dr. De Brabander, please.

Dr. De Brabander

569. Yes, I agree with what Dr. Boobis said, it completely described what validation is of a analytical method. Of course I don't have experiences with assays for very low amounts of oestrogen in blood, we don't work in blood, but it is completely described. The most essential thing is specificity – that you are really measuring what comes up, and in that respect yesterday we talked about qualitative and quantitative methods in risk assessment, we have the same nomenclature in analytical chemistry, qualitative and quantitative methods, and both are always mixed. Every quantification needs a qualification; you must be sure of what you are counting; the specificity of the method is extremely important. And also, if you have a qualitative method, you get always a signal and you get some kind of quantification, but it is only qualitative and again, you will have to fit the rules for quantification, a calibration curve etc. etc. I can put at your disposition a number of papers on validation, but I don't think we will start a discussion on validation as it is strictly described.

Chairman

570. Thank you very much. Any other experts? US.

United States

571. And then, just as a follow-up, if in Dr. Boobis's opinion the Klein assay has indeed been validated by any of the evidence that is on the record.

Dr. Boobis

572. Not to my knowledge. I would just comment on my concerns about the Klein assay. There is a review published in the Journal of Paediatric Endocrinology and Metabolism in July of this year by the Klein laboratory, or with Klein as an author I should say, and it states in the review summary: prepubertal boys have oestradiol levels of 0.4 plus or minus 1.1 picograms per ml – which is somewhat higher than the level that was reported in the 1994 paper, which was 0.08 picograms per ml, that is significantly different. Now the Klein assay uses a recombinant assay in yeast with the human oestrogen receptor and therefore it is not specific to oestradiol-17β; if it is, there is something strange about the biology, because one would not imagine that that receptor could discriminate between different oestrogens with absolute certainty, because otherwise the whole concept of oestrogenicity would not work. There are extraction procedures in the assay which might help select out certain compounds or others. Having looked at the characteristics of the assay, I find it extraordinarily difficult to understand why that assay would be so specific, or so sensitive, to oestradiol as opposed to other oestrogen agonists. There are other assays based on the recombinant oestrogen receptor; one of them utilizes a mammalian cell, not a yeast cell, and it is by Dr. Paris's laboratory. They have reported, using this assay, levels of oestradiol, of I think a couple of picograms per ml, yes, 1.44 picograms per ml. So we can see now that using these recombinant assays there is a variation from below 0.1 to 0.4, to 1.4, so that my view, having looked at these data is that, first of all, the recombinant assay has not yet been validated adequately, but secondly there is evidence, when one looks at these data, to suggest that the circulating levels of oestradiol in male children are lower than previously thought, I would accept that, but I would not think they are as low as in the original publication by Klein *et al*, because there have been numerous publications since then using a variety of assays which suggest that the levels are certainly higher than those very low levels first reported.

Chairman

573. Can I give the EC and then Dr. ...

European Communities

574. Gentlemen, I think we have a different interpretation of the data, and we will review references made by Dr. Boobis and will reply to that on Monday and Tuesday, but we understand that all the latest assays, and the one mentioned by Dr. Sippell later on, from the professors in Montpellier, they confirm that the level of oestrogen is much much lower, many more times lower than the ones reported in the JECFA report. There is no doubt, and even Dr. Boobis in his reply says in the first sentence of his replies that there is no doubt today that the levels are much lower. This minor difference to which he has made reference, they are not statistically different important differences, they are minor differences which sometimes you observe in the assays, and if you normalize the assays, you will see the values you expressed in the different assays, you will see there is no doubt about it, that it is significantly lower. But I have to move on from that debate and come back again to Dr. Sippell, and other scientists may come in, for example. In the risk assessments which the European Communities has performed and which you have in your files – and I refer to our 1999 and again to 2002 assessments – do you think that the European Communities has attempted to evaluate the risk for the prepubertal children from exposure to these hormones, taking into account these latest values which have been measured by the most sensitive assays?

Chairman

575. Dr. Sippell.

Dr. Sippell

576. I think that the risk is, and I have read several papers on that and also from my clinical experience, that as I pointed out yesterday, the levels probably are still lower than what has been measured by a radio immuno assay, and that the recombinant assays, they might differ, but they are with a lot of indirect evidence much closer to the truth than the traditional assays that we are all using nowadays in a routine lab. And if you calculate, then the exposure certainly is much higher if you have the low levels with the recombinant assays as a basis, and therefore I think some people have calculated that as little as 10 grams of meat ingested per day for a prepubertal boy might be or will be above his own production rate, and this is something one should consider.

Chairman

577. Excuse me, I don't think the US questions have been fully answered, so may I invite experts other than Dr. Boobis to add their comments on the first part of the US question and then move into the second part of the question. Is there any expert who is willing to add comments on the first part, on validated or not.

Dr. De Brabander

578. Well, as I said, there are rules for validation and normally if a lab performs well it is controlled by some organization. I don't know, I tell just for Belgium, you have the Belgian accreditation system, and labs who work in accreditation regularly have inspection from auditors. I have experience with that because I am an auditor myself, trained as an auditor, and when I go to a lab and they have qualitative methods (of course you don't test every method every time) I ask samples to be analysed. For example if it is urine and they have a method for testing urine, I ask them to prepare some samples of urine and I ask the components and then I take out amounts of the components and put them into the urine and then say do the test and show me the results. And then you can say that your method is validated. Of course, there are rules on paper – but in practice you can see if it works. And if it does not work, you can get the feedback to the lab – that's not in order, you should do that; that being the validation. It is not that you just have paperwork, there is control, and if you have a lab that works on GLP or accreditation, you have laboratory control on the results. In addition, maybe what was said, that a method is good when it is done in two labs, we use that also, performing analysis in two labs, and you see that for us chemists is it normal that if you get, for example, one ppb in one lab and two ppb in another lab, that's nearly the same. They are using slightly different procedures and it is within the variation of the method. And there is also evidence for that; there is a curve published by Horwitz, from the United States, who says that the uncertainty goes up when the concentration goes down.[3] The lower the concentration, the more difficult. Of course, you can understand that it is really impossible to have exactly the same figure. So the figure may vary a little bit within ranges, giving the same results.

Chairman

579. One follow-up question. In order for this scientific data by one laboratory to be validated, do we need a kind of endorsement by another laboratory or a number of laboratories on the same data?

Dr. De Brabander

580. No, it is not necessary, you have different systems, like I said, you have an accreditation organism who control that your lab is accredited. Within the accreditation you are also obliged to do

[3] W. Horwitz, L.R. Kamps, K.W. Boyer, J.A.O.A.C. 63 (1980) 1344-1354. (Reference provided subsequently).

ring tests. There are organisms who will prepare samples with certain amounts of components, the laboratories that are accredited need to analyse those samples and produce results. If your results are outside of a certain z-score[4], as they call it, outside the normal range, you are alerted, and if you come, during an accreditation audit, you can ask: can you give me the results of your ring test, how have you done for that component, how have you performed for that component, you can control that. And that's not another laboratory, that's an organization who controls it. I hope that answers your question.

Chairman

581. Dr. Boisseau.

Dr. Boisseau

582. Thank you, Mr. Chairman. Yes, I would like to confirm what Dr. De Brabander just said. However, we are talking about two different things here. We need to draw a proper distinction between the accreditation of a laboratory and the validation of a method. Dr. De Brabander has just spoken of an accreditation, and I have nothing to add to what he said. But, the question that was asked concerned the validation of a method. Dr. Boobis had reminded us of all the internationally recognized criteria for validating a method, and as Dr. De Brabander said, it is well known that the lower the target in terms of concentration, the greater the uncertainty and the lower the reproducibility and the reliability of the method – this is well known. There are two ways of validating a method: there is intra-laboratory validation, which takes place within one and the same laboratory, i.e. it is the same laboratory that repeats a certain number of dosages at different periods with different technicians, and if the results fall within an accepted range, the validation takes place within the laboratory. But more importantly, there is inter-laboratory validation, in which a certain number of laboratories are selected within the framework of what is known as a circular test, and the method is tested for precision, reproducibility, reliability, and what is also known as strength to see if it is exportable from one laboratory to another. Thank you Mr. Chairman.

Chairman

583. Thank you. Ambassador Ehlers has a follow-up question.

Mr. Ehlers

584. Thank you very much. The question has basically three elements. The first one is: do these hormones accumulate in the body or does the body eliminate them in total or in part? If so, do the adverse effects depend on this accumulation or not? And thirdly, if they do, then if you start with a lower endogenous level, would you not say that the risk also diminishes? Thank you.

Chairman

585. Dr. Boobis.

Dr. Boobis

586. The hormones don't accumulate to any appreciable extent in the body because of the natural production of similar or the same hormones, and these hormones would not be able to function if they accumulated in the body. So we have evolved mechanisms to allow the turnover of the hormones.

[4] In statistics, a standard score (also called *z*-score or normal score) is a dimensionless quantity derived by subtracting the population mean from an individual (raw) score and then dividing the difference by the population standard deviation. (Explanation provided subsequently).

All hormones have to have a turnover so that we can switch on and switch off the signalling pathway as necessary to off-regulate or down-regulate the target receptor system, and that would be true of the xenobiotic exposure to the hormones as well, because once they are in the body, the natural hormones are indistinguishable from the native hormones and would be eliminated by the same processes.

Chairman

587. Dr. Sippell.

Dr. Sippell

588. Again, the special situation in children before puberty – there is evidence that for instance secretion of sex steroids is pulsatile on a very very low level and that the sensitivity of the organism is such that these extremely low levels are being picked up and being recorded in the centres, in the hypothalamus, so in the brain, and also in the pituitary for regulation, also for imprinting. And we know that prepubertal boys or prepubertal girls, in case of oestradiol, are particularly sensitive to very very low exogenous levels of oestrogens. We have, for instance, the natural example of Turner syndrome girls who lack ovaries and thereby ovarian function and thereby have no endogenous oestrogens. And we know that with as little as 25 nanograms per kilogram body weight per day we can promote growth in these poorly-growing girls. So I think if you make the point that levels are very low, then at the same time sensitivity is of course adjusted to these low levels, which has to be taken into account also for exogenous exposure.

Chairman

589. Yes please …

Mr. Ehlers

590. Yes, thank you, I followed that explanation and there is part of my question that has not been answered yet, maybe somebody can do it. That is – since the body eliminates, then there is no accumulation, or if it is only temporary until the body has done its work, the adverse effects then do not depend on that. But you were trying to say that the fact of starting at a lower level does not diminish the risk but it keeps it at the same rate.

Chairman

591. May I give the floor to Madam Orozco to follow-up on the question.

Ms Orozco

592. Would there be any comments to the follow-up question of my colleague before I change the subject? Because I would ...

Chairman

593. I will give the floor to the US first and then the EC. EC.

European Communities

594. When we started the meeting, if we think of a fair distribution of time, I think they have been asking quite a lot of questions and we don't have the time to ask our questions.

United States

595. I think this is a very quick question if the Panel will indulge. Yes, it is related to Dr. Sippell's response. Very quickly for the members of the expert panel who have had experience in JECFA, that is Dr. Boobis, Dr. Tritscher, Dr. Boisseau, Dr. Wennberg, I am wondering, does JECFA in its evaluations take into account populations such as prepubertal children or sensitive populations, and how do they do that?

Dr. Tritscher

596. It's a basic principle of every risk assessment to take – it's a general remark – to take into account sensitive subpopulations, it's a basic principle. Because that is the part of the population that you want to protect with what you are doing, and this is based on the availability of data, what is taken into account. But it is definitely it's the goal of the risk assessment to identify who would be the most susceptible, the most sensitive part of the population, and that is the part of the population that the risk assessment is targeted to.

Ms Orozco

597. Just a quick follow-up question: how was it done in the 1990 evaluation?

Dr. Tritscher

598. I cannot respond to that question. I am not entitled to respond to that, sorry.

Chairman

599. Dr. Boobis.

Dr. Boobis

600. The Committee had available to it studies conducted in developing animals, where one of the assumptions is, based on research and scientific information, that the basic physiology of the test species that were used has a similarity to that in humans, and based on an evaluation of effects in those sensitive life stages, together with the other available information, the Committee concluded that it had been possible to evaluate the risks to all susceptible populations.

Ms Orozco

601. One more question, Dr. Boobis. How was the endpoint chosen in the 1990 evaluation?

Dr. Boobis

602. One of the hallmarks of a toxicological evaluation is that we don't focus on a specific endpoint because of the concern that we would miss something. So we use, as much as possible, to start with a so-called holistic approach, so we look at the totality of effects, evaluating multiple endpoints for the possibility of a compound-related effect. So in this case we looked at reproductive outcomes, we looked at the developmental effects and we looked at a range of other effects that were the normal hallmarks of reproduction and development in an animal.

Ms Orozco

603. Just one more question. The ADI that has been established – is that protection enough if you would take into account the new data about sensitivity of prepubertal children?

Dr. Boobis

604. I have done a calculation, which was in my responses to the questions, based on what I consider a consensus concentration that was somewhat higher than the lowest concentration, but was still significantly lower than that originally reported, and I calculated that the ADI would still be protective. I should add that what has not been mentioned so far is that we should not just take the external exposure and assume this translates into an internal dose or concentration. There are two factors which go against this. One is the pre-systemic metabolism we mentioned earlier – I think it was assumed this was 100 per cent in the EC evaluation, sorry, zero per cent, it was all absorbed. Whilst I accept that it is likely lower than in an adult, it will be very unlikely to reach zero per cent, particularly after the first week of life, and there will not be exposure to the hormones in meat in the first week of life as I understand it. And the second is that the hormone is not circulating completely free, a very appreciable amount is bound to sex hormone binding globulin and other proteins and there is good evidence that only the non-bound form is able to cross cell membranes and interact with the oestrogen receptor, and so that will reduce the circulating concentration as well. So that one has to consider those aspects in the evaluation.

Chairman

605. OK. Canada wanted to ask a related question quickly and then we move back to EC.

Canada

606. Yesterday there was some discussion about the extent to which the human population is exposed to exogenous sources of hormones in their diet, and Dr. Boobis yesterday indicated that there was a significant amount of exposure to oestrogens or to phyto-oestrogens or oestrogens in plant material, and my question then to the experts is: in establishing the ADI, is the extent of exposure to exogenous hormones taken into consideration, particularly in the diet of a prepubertal person, and is there any evidence that in the normal food, a diet with a normal food consumption, that prepubertal boys are at risk from exposure to exogenous hormones?

Chairman

607. Thank you. Dr. Sippell.

Dr. Sippell

608. I can be very brief. I believe that nobody has ever investigated this probably, also due to the fact that this is extremely difficult, also ethically, as I pointed out yesterday.

Chairman

609. OK. One more.

Canada

610. Dr. Sippell, in 2001, I believe, you co-authored an article that was looking into precocious puberty and you indicated, I believe, in your conclusion that there was no evidence in the literature

that exogenous exposure to oestrogens led to pseudo puberty, which is to be distinguished from central puberty. But I wonder if you could elaborate on that conclusion that there was no evidence in the literature to suggest that exogenous exposure to oestrogens cause precocious puberty?

Dr. Sippell

611. Yes. This was, as you just said, more than six years back – I think that meeting was in 1999 – and this was a review article, so we combined a little bit of our own research with the opinions published in the periodic review literature. And at that time we came to that conclusion. Since then the acceptance of the significance of the supersensitive oestradiol assays within paediatric endocrinology increased tremendously because, as I said before, it for the first time gave an explanation for basic physiological peculiarities which we did not understand before, and therefore there has been really a change of our understanding since then, and therefore my opinion now is quite different from that opinion in the one review article you cited.

Chairman

612. I will give the floor to the EC.

European Communities

613. Chairman, I said that I had two related questions to ask. First, it is not disputed that oestradiol produces a number of metabolized and other substances when administered to animals, and quite a substantial part of this is in the form of this so-called fatty esters, or lipoidal esters, which are thought to be eight times more potent than oestrogen itself, and we know that from the review of JECFA papers that the potential risk from these esters have not been taken into account in order to measure the effects on the humans when they are administered This goes back to Dr. Boobis, to what he said. He explained how they have taken into account the prepubertal children. Here we are not talking about developing animals, that's not the point, the point here we are talking about is developing human beings, boys and girls, and we cannot extrapolate from developing animals, which we know nothing about their organism, and draw a conclusion about human beings which nowadays it is internationally agreed, and Dr. Boobis has also said, that is at a much lower level of production. By the way, we have gone through the JECFA report and we didn't see any reference to developing animals. They have done the classical type of tests which are on animals, as they do it, and so all this is really questionable, and if there is any different view, then all the scientists can take the floor. The most important metabolite, which accumulates in the fat of meat, the fatty esters, which are more important, they are not taken into account. You cannot extrapolate for young animals, here we are talking about human beings, and this has not been done. And Dr. Sippell has confirmed, and if you would like to intervene, if you wish to explain why this is significant, and I posed the question in the beginning, we have provided the evidence, it is our 1999 and 2000 risk assessments. We have tried to estimate what would be the effects on prepubertal boys and girls, taking into account these recent findings from the residues in meat treated with hormones, under normal exposure conditions. And here we are talking about normal exposure conditions, we are not talking about other kinds of exposure which make up from misuse and abuse, we will come back to that later on, that is not the question. Here we are talking about normal exposure conditions. Thank you.

Ms Orozco

614. I would like to ask, because I think it is a very important issue that is being touched right now and it was asked before, and I would like to hear answers from as many experts as we have, as to whether the EC evaluated the risk to prepubertal children from the exposure of eating meat from treated animals. I think that is a very important question for the parties and for the Panel on which to hear views from the experts, please. And I am talking about the risk assessment, that is the three

Opinions that have been submitted by the EC and the supporting studies, I think that is the limit of their assessment for the purposes of this exercise.

Chairman

615. Dr. Boobis.

Dr. Boobis

616. The EC estimated the possible exposure of prepubertal children to food-derived hormones making a number of assumptions which we could debate here; they were certainly conservative, let's put it that way. For example, that everything that they were exposed to would be absorbed into the circulation – that is a conservative assumption, you could not get more than that but you could certainly get less than that. But what was not done was to consider what would the actual risk be, this was an exposure evaluation, I could not find in the documentation what the adverse effect that they were comparing that exposure to would be. So certainly they have done an evaluation of potential exposure, with certain assumptions, but I could not see how that was a complete risk assessment in those populations. Just to add, if they wish to refer to page 70 of technical document 43 of JECFA, you will find reference to the reproductive toxicity studies that were available for evaluation.

Chairman

617. Turning to the JECFA recommendations, how would you comment on Dr. Sippell's response indicating that scientific material referred to by the EC requires the revision of the Codex recommendation with respect to oestradiol. In the replies of Dr. Sippell to the Panel's question 42 there was a statement that scientific material referred to by the EC requires the revision of the Codex recommendations with respect to oestradiol. This a comment by Dr. Sippell. Are any other experts willing to add their own comments on this statement? If none, EC.

European Communities

618. Chairman, I think we can provisionally make a little connection to this issue by making reference to the dose response, which is also important to understand, because children indeed are a very sensitive segment of the population, this is not disputed, and it is not disputed that they have much more lower level of endogenous production. And it has been said yesterday, for example, that here we are not talking about zero risk because the risk is non-appreciable, but the concept non-appreciable does not mean zero risk. There is some risk and we have heard that it is not possible to calculate it exactly because the shape of the curve is not clearly defined, we don't know how it is defined. We have evidence and the scientists which are around me can take the floor if they wish to explain in more detail. The question is the following: we know and we have observed – the scientists and experts and the studies which we have submitted to the Panel and in our risk assessment – with the exposure already to the background levels, endogenously produced, we observe a biological action, several biological actions on the organism of young children. Some of them may lead even to cancer, this is not also disputed. So the question is: since we know this already and we have evidence, a few molecules, one or two or three, in the experiments already initiate the cells to grow and proliferate and divide, the question is how does this enter into the risk assessment of JECFA in this particular case of residues in meat from animals treated with hormones for growth promotion? This is a very specific question. Because we have tried to take this into account in our risk assessment and came to the conclusion which is now in our documentation. The point I make is I don't want to fudge the issue, this is taken into account on page 70. It is very precise, knowing that a very small, limited number of molecules, one or two, have a biological action on the organs of young boys and children. Why was this not taken into account when JECFA has evaluated these hormones? And is

this an important element to take into account in the light of the new evidence which is now available, for example, by JECFA?

Chairman

619. Dr. Boobis first and then US.

Dr. Boobis

620. Chairman, I must seek clarification. I am not clear yet whether the question relates to the DNA reactivity of oestradiol or to the hormonal effects of oestradiol. So far, what Dr. Sippell was talking about, as I understand it, was the hormonal effects. The genotoxicity argument is an additional argument and I was not clear in my own mind as to what was being asked by the EC.

Chairman

621. Would you like to clarify first?

European Communities

622. Chairman, the debate about the genotoxicity data is separate indeed, in our statement, what we are discussing here is about the hormonal effects, the effects through the hormone receptors' mediation.

Chairman

623. Thank you. Dr. Boisseau.

Dr. Boisseau

624. Thank you, Mr. Chairman. When it comes to the hormonal effect on pre-pubertal children exposed to hormone residues, and I am speaking of natural hormones, I think we need to recall the context of these discussions and to separate oestradiol, for example, from a xenobiotic, because when we say that an adult or young person is exposed to residues, we need to know what residues we are talking about. Since there is an endogenous production in the animals consumed for which we need to make allowances, what we are talking about is the additional residues linked to the treatment. Even if there is no treatment, there is in any case a basic level of residues that are natural. So what I want to know is, in view of these well-known variations in residues that are naturally present in meat, what is the risk already identified in connection with these residues alone and what is the additional risk linked to the supplementary residues resulting from the treatment. Oestradiol must not be treated as a xenobiotic on an all or nothing basis. The problem of oestradiol is that whether or not there has been treatment, we are still exposed to residues, and we must not forgot those residues.

Chairman

625. US.

Mr. Ehlers

626. Thank you. That is similar to what I was going to ask, not only about beef but about other sources, eggs or vegetables or others that also have hormones that come into our – or to children's, for that matter – diet. Do we have to stop their consumption of all of those also? Because if the effect is very great by just a few molecules, then it is not only the beef that is treated with these hormones, but

all other sources should also be stopped. Do we have to set an age limit for consumption of any beef, any eggs, any broccoli or whatever other source of these hormones exists in nature?

Chairman

627. Any experts? Dr. Guttenplan, please.

Dr. Guttenplan

628. Not a direct answer but a clarification. When the term "a few molecules" is used, that really is a simplification. It is not a few molecules, it's a small number of molecules per unit of whatever unit, usually its weight that you are talking about. So it isn't that if you have one or two molecules you are going to have a biological effect, it's basically a low concentration, I think this is what the EC is referring to, and not a few molecules.

Chairman

629. But still the question remains to be answered. No expert? Dr. De Brabander please.

Dr. De Brabander

630. I cannot comment on risk assessment because I am not a specialist in risk assessment, I would just comment on the broccoli Mr. Ehlers mentioned. You know that for young children all kinds of these things should not be given because they contain some natural thyreostats which are not good for young children – for thyroid function, yes. Some food should be forbidden for young children, including broccoli.

European Communities

631. Chairman, here the point is that there is no valid reason to overburden the human body, in particular of young children, with other sources, exogenous sources of these substances if it is not necessary. Normally we do it with children when it is for medical treatment, when there is a necessity; here there is no necessity to do it. But I would like to ask Dr. Guttenplan, and his qualification was very useful, this small quantity of molecules that you said, would they be present taking into account the ADI which has been fixed and the MRLs, if that quantity has just been fixed by JECFA, would that be sufficient to agree that a small number of molecules can indeed initiate or promote cancer? Would that be sufficient in the small quantity which has been defined as an ADI or an MRL?

Dr. Guttenplan

632. You are asking whether the ADI that is currently accepted is sufficient to protect against cancer. Is that the question?

European Communities

633. Yes, we have turned the question another way. My question was: if we agree that a small number of molecules, not one, two or three as you said but nevertheless a small set of molecules, can indeed initiate biological action, cells brought into separation and division, would the quantity which is included in the ADI from the residues in meat treated with hormones, would that quantity of molecules that can come from the absorption of these residues be sufficient to give rise to this kind of biological action when eaten?

Dr. Guttenplan

634. If you are talking about cancer, I don't believe there is a risk from consumption below the ADI for cancer. Those low levels might have a greater effect on developmental abnormalities in children though – I think Dr. Sippell has commented on that already.

European Communities

635. So you would agree that there would be other developmental effects on children, but probably you don't know if that will be leading eventually to cancer?

Dr. Guttenplan

636. I don't think that the levels that produce developmental effects in children, that might produce developmental effects in children, would be sufficient to induce cancer later in life.

Chairman

637. Dr. Boisseau would like to add?

Dr. Boisseau

638. Thank you, Mr. Chairman. Very quickly, the statement by the European Communities that there is no reason to overburden an intake of residues clearly has to do with risk management. Here, we are talking about risk assessment, and I think it is important to separate the two concepts. When we say that a few molecules could possibly generate tumours, excuse me for saying so, but we are talking of induced hormonal cancers. I think that there is currently a consensus that cancer associated with hormonal activity can give rise to a threshold, so we must stop speaking of a few molecules, since in the case at issue, we are not talking about induction, we are talking about genotoxicity, in other words promotion. And I think that there is a consensus on the fact that there is a threshold effect: this has been confirmed in writing by many committees. Thank you.

Chairman

639. The focus of our discussion at this point of time is scientific evidence in terms of risk assessment in general. Dr. Wennberg would like to ...

Dr. Wennberg

640. Just to recapitulate what I was saying yesterday about the additional residues that could be calculated from the residue depletion studies, where there were animals which were treated and animals that were not treated, the concentrations of the three natural hormones were analysed – what the excess amount of hormone would be in the beef – and compared to the ADI. The figures which are in the JECFA report and also in our report to the Panel say that the total oestrogen highest excess would be in the range of less than 4 per cent of the ADI, so that is a very small amount of the ADI. For the progesterone, the additional residues from the treatment would be 0.003 per cent of the ADI for progesterone, and for testosterone it would represent around 0.2 per cent of the ADI for testosterone. So we are talking about, in these studies, where there were control animals and treated animals, where there was variability in the natural hormonal discharge from these animals, that it is quite a small amount which could be considered additive to the natural background levels.

Chairman

641. Thank you. Yes.

European Communities

642. I would like to ask the representative of JECFA, do you know the date of these studies? Since when do they date? Because we know that these data date from the 1970s and 1980s. Could you give us the date of the studies to which you refer? We have been asking for this data, to see them.

Dr. Wennberg

643. These studies are available publicly reviewed by the committee with individual animals so you could have studied them all by yourself in FAO Food and Nutrition Paper 41/12. These are studies which were provided to the committee by the Food and Drug Administration of the United States and were the studies that were used for the authorizations for particular products containing these substances. If you consider that these studies were not sufficient for the authorization of these hormones in the United States, I think you should ask the questions to the United States. Thank you.

Ms Orozco

644. Excuse me, I have a follow-up question, please. What is the date of the residues data JEFCA used in the re-evaluation report of 1999? Or maybe, because we don't need a list of all the information used, but maybe to cut short the question, did you have new residues data for the 1999 re-evaluation? Did you use any residues data that was not used before?

Dr. Wennberg

645. Yes, as I was saying, for the 1999 evaluation the data that was reviewed, that was not reviewed before, was the complete set of residue depletion studies that were provided by the Food and Drug Administration of the United States. Now these had not been evaluated before by JECFA.

European Communities

646. Chairman, on this point, because this is important. I refer, and it should be in the records of the Panel, to Canada's Exhibits 17, which is the residues analysis monograph prepared for the 1999 evaluation by JECFA. It is on the record. Canada's Exhibit 17 and I refer to pages 88 and 89, where the studies upon which the evaluation was based are cited. And I don't see any of these studies cited here that it is more recent than 1989, they all date to 1979, 1982, and quite a number of them are undated and unpublished, so presumably they date from the 1970s and 1980s. I don't see any studies of the date which the representative of JECFA and Codex cite now. It is on the record.

Mr. Ehlers

647. Thank you very much. I would like to add another point to this. First of all, of course, what is at stake here is not the JECFA studies themselves but rather the EC risk assessment, that is what we have to study. But perhaps the question more likely should be whether since the 1999 study to now new information has come to light that would question, undermine or require that a re-evaluation be made now in the light of new information that has appeared since that re-evaluation of 1999. So this would be my question to everybody. Has new information come to light, new studies, that would indicate that the basis for the 1999 re-evaluation has changed so much that a new evaluation is needed now? Thank you.

Chairman

648. Thank you. In addition to that I am posing this question to JECFA: whether or not the new data available in the 1999 assessment were publicly available since that time? In order to know what was the reason why the EC has not received all these data materials since that time.

Dr. Wennberg

649. Thank you, Mr. Chairman, but I think that we are in the wrong, reverse sort of situation here. It is not for JECFA to submit data to the EC, it's for the EC to submit data to JECFA if they want JECFA to evaluate anything. So the data which are the basis for these percentages that I was quoting before are available in the report of JECFA, so they are available to everybody and not only to JECFA. That is the point of JECFA, to publish the evaluations.

Chairman

650. Does this include the new data that is not those produced in the 1960s and 1970s?

Dr. Wennberg

651. Well, as I now look at the reference list, many of these studies are from the 1980s and some are from late 1970s, some are not dated, but it's not true to say that they are all from the 1960s and 1970s. But may I also say that even if they were older, if the methodology that was used, and if the methods had been validated properly, there is no reason to discredit any studies because they were done a long time ago.

Chairman

652. But my question was that JECFA said that new data were also reviewed and that all those data were publicly made available. I am wondering whether those new data were also publicly made available. If that is the case, then there is no reason why the EC is continuing to claim that it has not received any new data other than that from the 1960s and 1970s.

Dr. Wennberg

653. The data that was evaluated by JECFA in 1999 as concerned the residues part are the data which had not been previously evaluated by JECFA. JECFA does not produce studies themselves, JECFA receives data from various sources, as we have explained before, from companies, from governments, from other institutions perhaps, and so what JECFA received and evaluated in 1999 was the complete residue dossier for these particular products, which are mentioned by name here in the report, from the Food and Drug Administration in the United States to JECFA. That was new data. It does not mean that all this data was produced in 1999, it means that the data was made available to JECFA for this evaluation, and there are studies from 1986, I read here in the reference list, 1979, 1982, 1983, 1989 and so on and so forth. I don't think I have to go further on this issue.

Chairman

654. Dr. Tritscher.

Dr. Tritscher

655. I would like to add just some general comments. As we have explained in our response to question No. 13, I refer to page 12 in our response, all documents from JECFA are published and are

publicly available in the public domain, all JECFA assessments, and I think that is one of the features of JECFA, to write very detailed monographs with very detailed descriptions of the database and complete references. In general, all these documentations are available within a timeframe from 8 to 12 months after the meeting, as printed versions. Due to this lengthy editing and printing process, we make draft monographs available to interested parties, to member states, based on requests, earlier if so done. With respect to data that are looked at again, JECFA does not create data as such, it reviews data. The call for data is always published approximately one year ahead, so the planning for each JECFA meeting starts approximately one year ahead. There is a public call for data out, where it is detailed very clearly what kind of substances are evaluated, for what purpose and what type of data the Committee would want to have. And just posting things on the Internet is a very passive way, so there are additional means of distributing this call for data, in particular through the Codex distribution lists. Member States, parties here, they are all represented at the respective Codex committee meetings, and they do receive via this means also the call for data. We cannot actively go out and retrieve, so it is the responsibility of the member States to provide available information, and that is then submitted to the secretariat, to the relevant expert and reviewed. Thank you.

Mr. Ehlers

656. Yes, I would just like to make sure, since nobody answered specifically what I asked, I take it then that the answer is there is no new scientific information that would fundamentally change what was already analysed in the 1999 review.

Chairman

657. EC.

European Communities

658. Mr. Chairman, I don't think one can draw this conclusion. I think the scientists should speak, each and every one of them, on this question, because it is very important. There should be no conclusions by default, I would guess.

Mr. Ehlers

659. That is why I put in those terms to see if I could actually.. .

European Communities

660. Could you put the question in a negative way so that we could also see the reaction of the experts, there might be another way of putting the question, please.

Chairman

661. Dr. Cogliano and the US and Canada.

Dr. Cogliano

662. The way the conclusion was just summarized by the Panel would not be my conclusion. We were not asked as experts to review all the scientific data that has become available since 1999, so I cannot make a conclusion. I certainly cannot make a conclusion that the data are sufficient for a new evaluation, or that the data are not sufficient for a new evaluation. That is not what the experts were asked to look at. I would say that it is normal that as new scientific data becomes available all different kinds of international bodies do take new looks at the data every few years. We have seen, I

think, the hormones were evaluated in the mid-1980s and then in 1999, so there seems to be that every 10 years or so there might be an accumulation of new data that warrants a new evaluation. But we were not specifically asked to look at the data and I don't think that any of us can really comment, or at least I cannot comment on the adequacy of the new data.

Ms Orozco

663. But most likely you have received all the information that has been submitted by the parties and drawn on the information that everyone has received from what has been submitted to the Panel. Is it your opinion that there is new information or is it your opinion from the review of all of that information that there is nothing new that merits a new assessment?

Dr. Cogliano

664. Speaking from the monograph meeting on hormones last year, these are again birth-control pills and hormone therapies at higher levels, there did seem to be some emerging data on genotoxicity for these hormones at those levels of doses. There seems to be lower levels of hormones in prepubertal boys than had been believed 10 or more years ago, there seems to be data about what might be happening at extremely low concentrations that contribute to uncertainty of the dose-response curves. Now whether those would fundamentally alter the ADI or change any conclusions, I think that is why you convene an expert group to evaluate all of that, and I don't think, I wouldn't feel comfortable making a snap judgement, that it is or is not sufficient to conduct a new evaluation. There do seem to be some new data but that's typical of all science. Scientists take the current state of knowledge and ask the next question, and at some point the answers may change, but I don't know if we are at that point at this time.

Chairman

665. OK. US.

United States

666. Thank you, Mr. Chairman. I think I glean from the Panel's question that the Panel was asking about residue studies in animals and whether new data had been put on the record regarding that aspect of the EC's risk assessment. I would like to ask the experts who have reviewed the data, has the EC put forward scientific evidence that supports the conclusion that previous residue data looked at by JECFA, for example, is no longer adequate or sufficient to assess the risk of the three hormones?

Chairman

667. I will give the floor to the experts first and then EC.

Dr. Boobis

668. To my knowledge I have not seen any new information on residues data on the hormones following their use according to good veterinary practice. There have been some new data on their use according to abuse scenarios and we need to discuss the relevance of that later I assume. But in terms of the standard residue package which forms the basis for a risk assessment, as far as I know there are no new data, and there are no reasons to believe that the data that JECFA evaluated were not appropriate for that purpose.

Chairman

669. Thank you. Dr. De Brabander.

Dr. De Brabander

670. Yes, Mr. Chairman, I think we all agree that there are no new data, and I just speak for the analytical part, the concentrations of the components etc. are produced in the years 1980, 1986 maybe, and it is a fact that analytical methodology in the years from 1986 on until now increased considerably, and it is not only the limit of detection which is decreased but also the separation power of components. You are able now to separate much more components from each other than in those days, and there are some examples, and I don't wish to go into analytical details, but you separate components in what we call a chromatogram, a series of peaks, and one peak can stand for one component but can stand also for two or three components, and if the analytical methodology improves, we see that suddenly a peak that was thought to be one component can split into two or three, and you can have three other components with different properties. I cannot, and it was not our job, and it is not possible just on paper, say the analytical data are not valid from that time, but you cannot be sure that they are valid because they are produced with methods which are not modern. It is not because they were validated in that time that they are still valid, because validation is a continuous process each time, that's why we as laboratories have to perform a new ring tests each year. We don't like that, we have to do it to keep up our performance, otherwise you say we perform one ring tests, OK, we are good for 50 years. That is not the case, we have to do it constantly, improve our methods and constantly improve our performance.

Chairman

671. US. Is it directly related?

United States

672. Dr. Boisseau has spoken of the issue of "old" data and whether "old" data is by nature bad data in his responses to the Panel's question. I though that would be a good follow-up to Dr. De Brabander's response.

Chairman

673. EC.

European Communities

674. Thank you Chairman. So Dr. De Brabander, if I have understood well, you are saying that these data which are old, from the 1970s and 1980s, because we have new, more powerful and more accurate analytical methods, their validity is in doubt because they are old and they have been measured with measurement methods which are by today's standards not credible, are not accurate. Is that the conclusion?

Dr. De Brabander

675. That is my conclusion. I cannot say that the data are bad, I don't say that, I just say you don't know that they are good, and you have to check them with modern analytical methods, but nobody performs that; we will not do experiments with melengestrol acetate because we don't have the means, we don't allow it and why should we do that, it is not our task.

Chairman

676. Yes. I would like to remind the delegations that we have 30 minutes before lunch break, but I have not given the opportunity to the other delegations so far to put their own questions. I am wondering whether the EC has exhausted, or almost exhausted, their list of questions under area 3?

European Communities

677. We have not exhausted the questions Chairman, but I can consider that the delegations ask one of their questions and then we can take the floor, if you agree.

Chairman

678. If you have – I see, OK. Dr. Boisseau first.

Dr. Boisseau

679. Thank you, Mr. Chairman. I wish to speak very briefly on the validity of the results obtained with methods that were used 20 years ago. What the Commission said is true as regards the results that are at the level of the limits of detection of the methods previously used. But once the results obtained are clearly over the limits of detection, what counts is the precision of the method and its reproducibility. The fact that the method used to provide these results is old is irrelevant to the extent that they have been validated. Indeed, we need only concern ourselves with the uncertainty that we may have regarding the very low values at the level of the limits of detection. Thank you.

Chairman

680. Dr. De Brabander, please.

Dr. De Brabander

681. On an analytical point, I would agree with what Dr. Boisseau says on veterinary drugs and xenobiotic agents, but not for hormones which are also naturally present and in the company of a lot of very similar components. You force me to go into a technical question, but a lot of molecules have the same molecular mass, it means that they weigh the same, but they have different structures and they are not easy to separate. So I know for a certain component like AED (androstenedione) and beta-boldenone we have to do a special procedure, separate them first in a liquid chromatogram and afterwards in a gas chromatogram, to separate the two components from each other, because you cannot otherwise distinguish them. That was technically not possible in the 1980s, so again I do not say that the data are not correct, I cannot say that because I have not examined them. You have got to be sure that you are correct, and it's not just the limit of detection, it is also the specificity, meaning the separation power of components has increased considerable since that year.

Chairman

682. Dr. Wennberg.

Dr. Wennberg

683. I think that maybe this is the final comment on this issue with the analytical methods. These methods which were used are also described in the report. The methods that were used were radioimmunoassay methods, which are very specific for the compounds in question at the time that

they were used. I don't want to go into the technical details here, but I think it is for the parties to argue whether these data are acceptable or not. For JECFA in 1999 they were evaluated and accepted.

Chairman

684. I see all the experts are waving their flags, starting with Dr. Boobis.

Dr. Boobis

685. I just want to make a point about specificity and that is the problem that Dr. De Brabander has just alluded to, which would in fact result in more conservative assumptions. That is, if you have cross-reactivity of your antibody detection system with something else, if that is not more potent than oestradiol or the analyte and it is hardly likely that it would be, then you over-estimate the residue present, so you are over-estimating your exposure. So while it is true that modern, very sophisticated analytical methods might allow you more precise estimates, my prediction is that the specific analyte would go down, not up.

Chairman

686. Thank you. Dr. De Brabander, please.

Dr. De Brabander

687. Yes, it is a possibility that concentrations go down, but there is also a possibility that they go up by other means. I had a colleague, I won't mention his name, neither the country, which has very very bad experience with radioimmunoassays. They did a radioimmunoassay and they say that animals are positive. They questioned the analysis, they did a separation and it was something else which caused a response on the radioimmunoassay. Radioimmunoassays are indeed – selectively but you can have cross reactions, you can have systems where the concentrations go down. Then I gave the explanation of modern methods, even in modern methods you have (in mass spectrometry, for instance) a phenomenon which is called ionization suppression. It means that when the component goes into the machine, it is not ionized and you don't see it and you underestimate the concentration. If you do a better separation, that ionization suppression is gone and you see the component and its real concentration. You have both: concentrations going down, concentrations going up, for modern methods corresponding with older methods. But again I would say I would not comment that the data are not valid, I don't know, and we don't know if they are valid.

Chairman

688. Thank you. Dr. Sippell.

Dr. Sippell

689. I can only agree with what was just said, and this applies particularly for the first period after birth. For neonates, for infants and for young children a standard commercially-available radioimmunoassay is not able to pick up the real concentrations, because there are numerous other cross-reacting steroids, for instance, that will really obscure the real concentration, for instance for oestradiol-17β. And therefore you have to do an extraction, you have to subject the extracts to a separation method, liquid column chromatography or HPLC, and then you have to quantitate, you can do that by either radioimmunoassay or by a gas chromatography and I think at the moment the new development is tandem mass chromatography, where you can have these separation procedures repeatedly and then, as Dr. De Brabander said, you separate many peaks and can quantitate them

accordingly. And I think the analytical methodology is consistently improving right now and therefore one should really look to the new data.

Chairman

690. Dr. Boobis.

Dr. Boobis

691. Mr. Chairman, the point has already been made that science moves on, probably in few areas more than analytical chemistry, where the advances in mass spectrometric techniques have been truly remarkable. But I would like to put in a point of pragmatism here. It is not possible to re-evaluate the residues data of veterinary drugs and pesticides every year, or every two years. The EU itself has a periodic review programme of pesticides which takes 10 years before a compound is rescheduled, and it probably takes longer because of the need to generate the data, so we have to live with the methods that are available. They have been validated, the immunoassays that were used at that time were validated for their purpose, which is not to say that there are not newer, better methods, but they were validated at the time, they were adequately fit for purpose. I would make the point that a method that is used to measure low levels of oestrogens in infants is a different question from a method that is being used to measure resides in food. The analytical challenges are quite different and the methods that were developed in the 1980s for the residues were fit for that purpose, and that is what they were used for. If you ask the question about the circulating concentrations, that is a different issue. So in terms of the residues the methods were suitable. We reviewed the data in 1999. It would be unrealistic to expect a complete new residues data package to be generated over a period of a few years because analytical methods had advanced. At an appropriate period of time in the future new data may be generated and it would not be unreasonable at that time to look again at the exposure data.

Chairman

692. Thank you – OK.

European Communities

693. But there are part of the file which the European Communities submitted to the Panel, and it is provided to you, Exhibits number 7 up to 43, among those Exhibits a number of papers precisely provide new data about the residues in meat from animals treated with these hormones for growth promotion. But not only that, these new data have been generated with the latest methods of detection and measurement, the most recent ones to which Dr. De Brabander has made reference. So then the question is why these new data which are available and produced with the latest methods available are not sufficient to lead JECFA to do a new evaluation? This is the first question. And why would the European Communities, who has performed such a risk assessment on the basis of those data, be considered not to be part of the latest data available that have to be taken into account, as were the old data of the 1970s and 1980s which were submitted to Codex? Thank you.

Chairman

694. Can I give the floor to Canada first and then to Dr. Wennberg?

Canada

695. Thank you, Mr. Chair. I have a question for the experts who have been involved in JECFA and it is a question of clarification between the type of data you use in a residue monograph and the

type of data you use in a toxicological monograph, and whether or not advancements in analytical techniques that relate to the type of data you would use in a residue monograph would have an impact on the data used in the toxicological monograph, which is the monograph from which the ADI is recommended. So a distinction between the two types of dataset, the dataset you would use for a toxicological monograph and the data set you would use for the residue monograph, and whether or not advancements in the analytical techniques, the types of studies you would do for residue monographs would have an impact on the type of studies that are looked at in the toxicological monograph from which the ADI is derived.

Chairman

696. OK. Dr. Tritscher.

Dr. Tritscher

697. Thank you. Going back to the graph I put up yesterday, the toxicological evaluation and the residue evaluation and then the exposure assessment are two different parts of the risk-assessment procedure, and there are different datasets underlying these procedures. In the case of veterinary drugs, for the residue studies there are metabolism studies, residue-depletion studies and so forth in the food-producing animal, so it is a different species, we are talking about cows, pigs, for whatever purpose the specific veterinary drug is registered. For the toxicological studies you have a completely different dataset and you look at normal test animal species, rodents in most cases, and in the case of the specific hormones we are talking about there were a lot of human data that were looked at in a toxicological study. There is some overlap, in particular with respect to metabolism studies for comparative purposes. If the metabolism is comparable in the test animal species, in the rodents, to what happens in the field, in the real application of the veterinary drugs of the food-producing animals. I think I will leave it with that.

Chairman

698. Would you be quick please.

Dr. Wennberg

699. First, I would like to respond to what the EC said about their data. As far as I can consider from the JECFA secretariat point of view, as I mentioned before, there was never any request from the EC to have these data evaluated. Secondly, it was up to the scientific experts which were appointed by the Panel to review the exhibits which were submitted by the different parties, so that does not have anything to do with JEFCA *per se*. And the final point I would like to make is that for the residue data that was evaluated in 1999, can I remind everybody that what was analysed was both the endogenous and the exogenous substances together, together with the metabolites that results from the elimination of the substances from the body of the animals, and there was no difference between what the natural production was as compared to what was administered. So there were quite high levels normally, so the point about low levels and more sophisticated techniques in this sense does not make any difference to the evaluation, because the levels were high in both cases and they were slightly higher in some instances when hormones were given, but the background level was quite high in both the control animal and the test animals. Thank you.

Chairman

700. Dr. Miyagishima, would you like to ...?

Dr. Miyagishima

701. Thank you, Mr. Chairman. I just wanted to make sure that the Panel is clear about the different roles of Codex and JECFA. As far as Codex is concerned, it has a built-in mechanism that would allow it to put in question the adopted MRLs, and in that case the procedure is through the inclusion of the compound in the priority list for re-evaluation. And the initiative should be taken by a member, and it is not for the Codex secretariat or other parties to take the initiative. Thank you.

Chairman

702. So having heard what the JECFA and Codex representatives mentioned, I think it is quite clear that it is for the members and not the secretariat themselves to request the new data to be evaluated by JECFA, Codex, right? That is quite clear. Canada please.

Canada

703. Yes, that's fine, our question was adequately answered. Thank you.

Chairman

704. So we have only 15 minutes to go before lunch break, but as I believe that a large portion of the EC questions have already been addressed, I will give the same opportunity to the US and Canada during the remaining time of the morning session and the afternoon session, and then come back to the remaining questions from the EC, if necessary, and others too. OK. I will give the floor to the US.

United States

705. Thank you, Mr. Chairman. A question to the experts who have spoken on the issue of genotoxicity of oestradiol-17β. I wonder, does the scientific evidence relied on by the European Communities in its Opinions support the conclusion that oestradiol-17β is genotoxic *in vivo* at levels below those associated with a hormonal response?

Chairman

706. The floor is open for comments from the experts. Dr. Boobis.

Dr. Boobis

707. I find it difficult to be persuaded that the evidence indicates such, because we have to be clear that the question of the genotoxicity of oestradiol-17β has been tackled in a number of different ways. Firstly, it used a variety of endpoints, a variety of test systems *in vitro* and a variety of endpoints *in vivo*, but more particularly it has used precursors of the presumed genotoxic metabolite. Quite frequently what has been administered is not oestradiol, it's one of the metabolites or the quinone product to an *in vivo* situation or even *in vitro* situation, and it is those metabolites that have generally given some indication of a positive result. Now it is my view that the genotoxicity of oestradiol *in vitro* functions other than by a DNA reactive mechanism of the parent or metabolite, that it may be through redox cycling, generating reactive oxygen species or per-oxidative products, and that as a consequence one can overcome in-built protective mechanisms of detoxication and repair by adding a high level, relative to the parent, a high concentration of the metabolite. So what happens is that you bypass a de facto threshold by giving that metabolite. And that is in my view what happens *in vivo* when these metabolites give a positive. These positives are not of, as I understand it, a mutational

response, they are a genotoxicity response, and so I would say that I have yet to be convinced that oestradiol 17β at low concentrations is capable of producing a genotoxic response *in vivo*.

Chairman

708. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

709. There is recent evidence where they have detected the DNA adducts, that means damaged DNA products that have been produced from the reaction of oestradiol with DNA in the urine. As far as I know this data is only submitted for publication. However, the levels are extremely low and I question whether such low levels have any significance with respect to cancer-inducing properties.

United States

710. Thank you, Mr. Chairman. As a follow-up, I think, to Dr. Guttenplan's comment, to the experts who have opined on this issue in writing, does the scientific evidence relied on by the EC in its opinions support the conclusion that oestradiol-17β is carcinogenic at levels found in residues in meat from cattle treated with the hormone for growth promotion purposes?

Dr. Boobis

711. I can be very brief, Chairman. I would say no, that I am not persuaded by the evidence presented that the levels present of oestradiol-17β in cattle treated for growth promotion have the capacity to produce cancer in those so exposed.

Chairman

712. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

713. We were asked to comment on potential, and the potential is there, but I think I agree with Dr. Boobis that in actual practice or in actual situations the risk is minimal.

Chairman

714. Thank you. EC.

European Communities

715. Chairman, can I have a follow-up to a specific point, just to clarify. So is it correct to understand then that we cannot say that there is no risk, but the risk is small, minimal as you say, but the risk is not zero?

Dr. Guttenplan

716. The risk is not zero. We really cannot calculate such low levels, but it might be less than one in a billion. But we were asked to calculate on potential, and I have a problem with that word potential in my responses. So it is almost like saying is it possible, yes almost anything is possible, but in a real situation – is it likely to occur at a significant level? – no.

European Communities

717. Thank you. This is, I think, an important clarification. Here we are talking about the residues from meat treated with hormones for growth promotion, and the reply was that the risk is not zero, it is small and it cannot be evaluated. So we are not talking about zero – I think it is important to clarify for the Panel and then come back with the question. In the previous panel which has examined the substances in 1998 there was another expert in the place where you now sit by the name of George Lucier, and he made an evaluation at that time that there would be a risk of one in one million from residues in meat, but then the subsequent Panel and Appellate Body reports said that his conclusion does not come from concrete examples, from concrete experiments he himself has conducted. So this statement which has been made is very important. The conclusion that the risk is not zero comes from residues in meat treated with growth hormones; it is small but we cannot calculate it. Could you please confirm this.

Dr. Guttenplan

718. Yes, that's right. It is small, we cannot calculate what it is. I might also say that every time we cook meat we produce new carcinogens, so every time we consume meat we are increasing the possibility that we will get cancer from the meat, but the likelihood is very small.

Chairman

719. Let me give the floor to Dr. Boisseau and Dr. Boobis and then back to the United States.

Dr. Boisseau

720. Thank you, Mr. Chairman. Concerning this carcinogenic potential associated with the hormonal properties of oestradiol, we come back to a general problem. When we carry out long-term carcinogenicity tests on animals, in order to be able to see anything, we have to use heavy doses which have nothing to do with the residue content in foodstuffs; if we used quantities more or less similar to the residue content, we would see nothing at all. In other words, as with the short-term mutagenicity and genotoxicity tests, we use high contents, and where there is a carcinogenic effect, we establish a relationship between the dose and the effect in the chosen experimental area. Once this has been done, and if indeed there is a dose/effect relationship, the problem becomes complicated, because we have to extrapolate from this experimental area to small doses in order to figure out whether there is a threshold and to determine the potential effect associated with a small dose. And at that point, we simply do not know what to do. Consequently, the JECFA like other committees, uses the principle of the safety factor. It is true that this is rather a simplistic system, and the truth is that it is open to criticism, because depending on the slope of the effect/dose ratio, the same safety factor will provide different levels of protection. But, as Sir Winston Churchill once said about democracy, it may not be an ideal system of government, but the other systems are worse.

721. Indeed, the mathematical extrapolation models will give you very different results based on the same data, depending on the model chosen and the criteria taken into account. So in the end, the pragmatic system that is used is worth what it is worth: it may not be perfect, but it is just as good as many others. Accordingly, when we say, as I have just heard, that when we have an effect/dose ratio following a carcinogenicity study and we cannot say that the risk is zero at low doses, the fact is that we simply don't know, we cannot say that it exists, nor can we say that it does not exist. So in order to protect itself and to protect public health, the JECFA opted for a safety factor of 1,000, in general, a figure which I think does provide guarantees – but we cannot make any claims, we cannot provide proof, nor can we cause alarm among populations, because in these cases we are not dealing only with hormones, there is all the rest, all the work that has been done by the JECFA for other substances, the work that has been done at the European Union level, since everybody works in the same way. So we

have to be careful about casting doubt on a general working method in the case of hormones, because there is no reason to stop at hormones. We would have to cast doubt on everything that has been done over the past twenty years. Thank you.

Chairman

722. Dr. Boobis.

Dr. Boobis

723. Thank you, Mr. Chairman. I wanted to make rather similar points and I will be brief. First is that my view is that the risk of cancer from the levels of oestradiol in its use according to GVP as a growth promoter is such that it is not appreciable. This is the definition of ADI, so I believe the threshold approach and safety-factor approach, which is widely used for compounds which are not direct-acting genotoxicants, is appropriate for this compound. And as Dr. Boisseau has pointed out, when we say not appreciable, it is because no risk assessor worth his salt is going to say zero risk, an absolute guarantee of safety. This underpins all risk assessment. If the policy makers, the risk managers, would seek an assurance of zero risk, then they should provide the methods to generate that assurance. These are not known yet and it is not clear to me how you would ever conduct a risk assessment and guarantee that, without ensuring zero exposure, and of course that would cease all use of all compounds where there is any risk whatsoever, and they all have some risk. Thank you.

Chairman

724. Thank you. Let me give the floor to Canada because I have seen the flag being raised since long time ago.

Canada

725. Mr. Chairman, if indeed the EC has a specific follow-up question rather than a running monologue and argument with the experts we can wait for their question and then we will pose our own question.

European Communities

726. Thank you, Mr. Chairman. It is not going to be a monologue but it's a precise question. Dr. Boobis, thank you for clarifying that non-appreciable does not mean zero, it is a small risk. But supposing it is one in one million, supposing that will come from residues in meat treated with hormones for growth promotion in accordance with good veterinary practice. Is this what you said?

Dr. Boobis

727. I would rather that words were not put in my mouth, Chairman. I tried to give my answers as precisely as possible, I hope they were clear. What I said was that there was a very low risk, I did not say it was one in a million, it could be much less than that.

European Communities

728. But it is not zero.

Dr. Boobis

729. I am talking about a potential, not necessarily a real risk, I am saying we cannot give an absolute assurance of the absence of risk. If that was possible I would be very enthusiastic that a risk manager would provide the methodology where that could be done for any compound whatsoever. It is the underlying principle of all risk assessment, within the EU and within JECFA and within all other organizations that conduct risk assessment of chemicals. I will not go into the details of risk-assessment methodology here, but one of the questions was did they use state of the art risk-assessment approaches at JECFA, and the answer is yes we did, and those approaches are still generally accepted worldwide as the most appropriate way of evaluating the risks of compounds to which humans are exposed.

Chairman

730. Thank you. The floor is for Canada now.

Canada

731. Thank you, Mr. Chair. Recalling the discussion of yesterday about the components of the risk assessment, and in particular the circumstances in which a dose-response assessment should be conducted. As a result of the absence of evidence that several experts have just indicated about the genotoxicity of oestradiol, is it your opinion that a dose-response assessment should be conducted in a risk assessment of oestradiol in this case.?

Chairman

732. Dr. Boobis and then Dr. Boisseau.

Dr. Boobis

733. Based on the weight of evidence evaluation of the genotoxicity of oestradiol – and I just wanted to clarify a point, I don't think that anybody on this side of the table has denied that oestradiol is an *in vitro* genotoxicant, there is no good evidence that it is mutagen, but it is certainly a genotoxicant *in vitro* – but based on the weight of evidence, the view certainly of JECFA was that that was due to a mechanism likely to have a threshold and therefore it would be appropriate and necessary to conduct a dose-response analysis of the *in vivo* responses, because any underlying mechanism would have a threshold in the view of the experts present.

Chairman

734. Thank you. Dr. Boisseau.

Dr. Boisseau

735. Thank you, Mr. Chairman. Let me just say a few words on the zero risk concept mentioned by the Communities. I merely wish to recall that, at least as concerns substances that are authorized and deliberately included as additives or as veterinary drugs, i.e. administered to animals, this zero risk concept was abandoned at least 20 years ago. It is valid today only for prohibited products for which, indeed, the most sensitive analytical method must be used to ensure that there is no fraud. So if I understood properly, as regards oestridiol and the carcinogenic risk associated with a hormonal effect, it is thought that extrapolation to low doses does not enable us to eliminate the least risk; but in that case, I repeat what I already said this morning, we must not lose sight of the characteristics of oestradiol, to name but one hormone, which is not a xenobiotic but for which part of the residue is a

natural result of the physiology of animals. So that if we infer that zero risk for the most minute quantities or oestradiol residues does not exist, then once again, what are we speaking of? Should we prohibit the consumption of bovine meat on the grounds that without treatment it will make a contribution in terms of oestradiol that could, if I follow this reasoning, generate a risk, however minute, but in any case not zero? Once again, even if we forget about the administration of oestradiol, the risk, however small, already exists in normal meat. We must bear this is mind, and this involves a quantitative evaluation of the risk, since even where oestradiol is not administered to animals we would – and I say this in the conditional tense – be exposed to that risk.

Chairman

736. I will give the floor to Dr. Tritscher and Dr. Boobis.

Dr. Tritscher

737. Thank you. I would like to make some general remarks and clarifications regarding dose-response assessments. The point to differentiate here is what we discussed already yesterday, I am sorry if I repeat something, but the difference between a qualitative and a quantitative dose-response assessment. A quantitative dose-response assessment requires extrapolation to the low dose range outside of the observed experimental studies. And this extrapolation down to low exposure levels requires a number of assumptions that go into a mathematical modelling to describe the shape of the dose-response curve in the low exposure range. And if this is possible or not with a reasonable level, an acceptable level of uncertainty and acceptable level of assumptions that go in, totally depends on the data that are available. It is not dependent on the compound, it is exclusively dependent on the quality and appropriateness of the data as a first instance. In this context I would like to point out that there is a lot of discussion regarding dose-response assessment and low-dose extrapolation in particular. And the International Programme on Chemical Safety has held an international expert consultation on dose-response assessment in general, and the experts define a six-step procedure for dose-response assessment where the first, maybe the first three, I don't have the exact layout now in my head, but the first three are in line, they end with the NOAEL and the ADI, because this is a dose-response assessment where no extrapolation to the low dose range outside the observable range is done. But then, depending on the quality of the data, the reliability of the data, you can do low-dose extrapolation. However, any low-dose extrapolation is mathematical modelling, it's the best-guess estimate. But this would allow a quantitative estimate of a risk, again, a quantitative estimate of a risk at a certain exposure level. But to achieve that quantitative dose-response assessment, you have to have the appropriate data, and I do not believe that in the case of the hormones the appropriate data are there.

Chairman

738. Thank you. Dr. Boobis.

Dr. Boobis

739. I just wanted to emphasize this generality of the acceptability of the concept of no zero risk. This is the EMEA's definition of an ADI for establishing maximum residue levels of veterinary medicinal products in foodstuffs of animal original, exactly congruous to the issue we are talking about. The ADI is the estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of body weight, that could be ingested daily over a lifetime without any appreciable health risk. So the EMEA, an organ of the European Union, has apparently not been able to come up any more than we have at JECFA or anybody else has, with a methodology that can guarantee the absence of any risk.

Chairman

740. Quickly, very quickly.

European Communities

741. Well, for the benefit of Dr. Boobis I should clarify the EMEA is just a sub-organ of the European Commission and it evaluates the substances for therapeutic treatment only, not for growth promotion. So this statement has no relevance whatsoever for the residues of meat treated with hormones for growth promotion. This is the role of EFSA. But Chairman if you allow …

Dr. Boobis

742. Does that mean that we can have zero risk in other circumstances, and could I ask the EC to provide a reference to where the methodology is so that I can apply it in my work?

Chairman

743. Excuse me, it is already five minutes past 1 o'clock and the interpreters won't be available from now on, so if you all agree, then, shall we resume our discussion in the afternoon with more questions by the US? The meeting will start at 3 pm here in this room.

28 September 2006, afternoon

Canada

744. Chairman, I have a point of order to make, and the point of order arose as a result of the brief display of what appeared to be a new piece of evidence on the projector. As I think I mentioned yesterday, we have seen this exercise as the Panel's chance to explore the issues to the extent possible with the experts. We have already exchanged through letters and through clarifications with you how we thought we might proceed, particularly in respect of the kind of argumentation and evidence that might be put before you, and you have already provided that answer and you have reiterated that answer yesterday morning. Over the last two days I think we have exercised considerable restraint in raising procedural objections whenever we have had statements more in the nature of arguments rather than questions; but I think it really is important to keep on track. What was on the screen we have not seen before, to that extent it is new evidence, and if the EC proposes to put forward new evidence, then we want a ruling from you that that provision of new evidence is simply not permitted. You have already provided that, you have already stressed that yesterday, and at this point I think it should go beyond a reminder, and it should be a ruling from the Chair. Thank you Sir.

Chairman

745. Thank you.

European Communities

746. I would like to make a point. This point can be made orally, it can be made better by means of a diagram, and it is in response to comments made by scientists this morning, it is not new evidence. If the Canadian delegation thinks that this will be considered as new evidence they have not seen, we can make the point orally. We thought that this way it was easier to understand the point which we would like to make. And it is in response to what has been said by scientists, so we are not submitting new evidence; it is the natural development of the dialogue in this room that we would like

to make this point. As I said, we can make it orally, we can make it through diagrams so everybody understands what one of our scientists said. That's all.

Chairman

747. Thank you. US has the floor first and then Canada.

United States

748. I would just make a quick point, Mr. Chairman, and then I am happy to move on with our questions as well. It is hard to say that a piece of evidence is responding to a question when there is a prepared power point slide, and I think, whether the evidence is oral or via some visual aid, I have to support the discussion of Canada on this issue.

Chairman

749. Canada.

Canada

750. Thank you, Mr. Chairman. I wish to underline that a point presented by scientific experts on the European Commission delegation is either expert testimony or it is new evidence to the extent that it is there to challenge what the scientific experts of the Panel have put forward. If the EC has a question to ask on the basis of what is on the record it may do so, but if it is a new point, then it is either extra testimony by the EC's delegation, or new evidence, and that is not permitted. Thank you, Sir.

Chairman

751. OK. EC.

European Communities

752. Maybe a point of clarification to the Canadian delegation. The Canadian delegation was referring to a paper quoted by Professor Sippell this morning, of 2001. I am not aware of this being on the record. Maybe Canada wants to comment on this.

Chairman

753. US.

United States

754. The paper by Dr. Sippell was actually cited in the US comments on the experts' comments, so it is on the record.

Chairman

755. Yes, you have the floor.

European Communities

756. Professor Boobis this morning has made a reference to a new paper by Klein, which we didn't know, and we have now found the data. Are we not allowed to make a comment on that? I don't understand what is the purpose of this meeting if we cannot comment upon something which has just been referred to.

Chairman

757. Before I answer that question, would you respond to the point made by the Canadian delegation just before, whether it is a testimony of the experts of the EC delegation or new evidence?

European Communities

758. Chairman, it is neither of the two. It is just a question through a means of presentation, or made orally; it is neither new evidence nor extra testimony.

Chairman

759. So, with that understanding, would Canada and the US delegation agree to the EC delegation moving on with their oral presentation on whatever issues they have, with or without the videotape screen?

Canada

760. Two points, Mr. Chairman. I understand first of all that as a matter of procedure I think the US is going to go next in questioning. It's impossible in advance of hearing the question to say whether we agree with the question as either expert testimony or a quote, unquote point. I don't know what that means. But very simply, if a point is being raised from outside of the record to question or to impugn what the experts have said, and we have not had notice of it, then we cannot respond to the point that is being raised by EC. That is the whole point of the procedural rules that are in place. So all I can say is that for your benefit, and to allow the process to go forward, we can agree to hear the question. We will reserve however our right to raise a point of procedure and then at that point to ask you to disallow the question. If that would help the process to go forward we will go along with that.

Chairman

761. To my understanding, whether to take a certain argument or presentation of the views or materials as evidence is up to the Panel. I don't know whether we as a Panel have to make a ruling on that procedural point at this particular point in time, but whether to accept it as evidence or argument or whatever will be decided by the Panel. So in order to prevent this process from being suspended or interrupted I hope the EC delegation will be very clear on this point so that US and Canada can agree on proceeding from here on. Would you further clarify on the point made by the Canadian delegation once again.

European Communities

762. Chair, to be deadly honest with you, I have not fully understood the point. Is the Canadian delegation saying that the EC cannot make its own experts or part of the delegation intervene to provide a scientific view on issues that have been discussed here? Thank you.

Chairman

763. I don't think that is the point. Canada has the floor.

Canada

764. I agree with you Mr. Chairman, that is not the point.

Chairman

765. EC.

European Communities

766. Would the Canadian delegate care to restate his point please.

Canada

767. Mr. Chairman, it's very simple. We see something on the display we have not seen before; the other experts here have not seen it before; we cannot respond to that. Now whatever it is, a point, piece of evidence, argument, expert testimony by one of the experts, we have not seen it before; we cannot respond to it. I don't know if the experts have seen it before. Something is being brought into this process from outside of the record and that is the simple point that we are making. If the experts on the EC delegation hear something that the Panel's experts are saying and they disagree; if there is something that they have said that does not fit within the record, then they impugn that, but they cannot bring in something that they have not seen before, that is simply not in accordance with the rules.

European Communities

768. Before you rule, can I provide a way out. We don't insist, we don't want to delay these proceedings any more, so we will not show this slide, but we would appreciate if we had the time later on for one minute to make the point orally, like we have been making comments orally the whole day yesterday and today, and we have not seen the comments nor heard Canada's comments and the arguments they were going to make orally either, we don't know what they are going to say now. We are in the same situation. So just to avoid the problem and avoid any delays, we are not going to show the slide in this instance to please and satisfy the Canadian delegation. Thank you.

Chairman

769. I think that is a quite positive response from the EC delegation, and I would like to remind all the delegations that the purpose of this meeting, as I mentioned in my opening statement yesterday, is to get the advice of the experts which the Panel has invited, for the Panel to get their understanding of the scientific and technical issues at hand. In that context, I think we are here to pose any questions or comments to the experts to get their understanding and advice, not in the form of a presentation of materials on evidence or whatever you may call it, so I hope delegations in putting questions do not get into the kind of exercise of presenting new evidence or new materials or new data. With that understanding, can the US and Canadian delegations agree that the EC delegation may have the chance to make their point a little bit later during our discussion this afternoon. And I will give the floor to the US delegation, as I mentioned this morning, because we have been stopped during our discussions when the US delegation was posing their questions. OK. US, you have the floor.

United States

770. Thank you, Mr. Chairman. Continuing on with the questions, I would like to shift gears and discuss the five other hormones at issue in these proceedings. To the experts with experience in risk assessment, who spoke on this issue in their answers: does the scientific evidence relied on by the European Communities in its opinions support the conclusion that it is not possible to complete a risk assessment for those hormones?

Chairman

771. The floor is open for comments or responses from the experts. EC.

European Communities

772. Thank you, Chairman. It's a question of order, I think. This is a risk management question, I think. This question, as it is posed, requires the scientists to say whether as risk managers we can do a risk assessment. I don't have any objections that the US poses this question, but he needs to pose it as a question addressed to risk scientists during the risk assessment, not to the risk managers. Thank you.

Chairman

773. Before giving the floor to the US, let me ask the experts whether they have any views or comments on this point. The question was posed to the experts first. Dr. Boobis.

Dr. Boobis

774. I cannot speak for the EC, and I think what has just been said is quite correct. I can speak for JECFA in which I participated, and in our view we had enough information to complete a risk assessment. I don't know if that is helpful, but that was the situation when we looked at the available data on those five other hormones.

Chairman

775. Thank you. Dr. Cogliano.

Dr. Cogliano

776. I think the way I would look at questions like this is that it is possible to complete risk assessments up to a certain point. IARC could do assessments of those, but IARC's risk assessment stops with the hazard identification and a statement about whether or not these hormones are carcinogenic. JECFA's assessment then continues to develop an ADI, which involves looking at the animal studies, selecting the dose where they think there are no observed adverse health effects, considering everything they can and dividing by safety factors. That's another more detailed risk assessment than IARC does. A further level of detail in risk assessment would be to do a dose-response curve down to lower doses and try to predict what would happen at very low levels, what would be increased risk, if there is any. And I think most people here have been very reluctant to say that you can extrapolate the dose-response cures and get any kind of precise level. So I think when we sometimes say can you complete a risk assessment, I think you cannot just say a risk assessment, but a particular type of risk assessment. I think you can complete a risk assessment that's an ADI style of risk assessment, you cannot complete a risk assessment that's a full dose-response curve and try to get a prediction of risk at very low exposure levels.

Chairman

777. OK. US.

United States

778. Then perhaps a good way to follow up would be to ask: does the scientific evidence relied on by the EC in its Opinions support the conclusion that any of these five hormones is carcinogenic at levels found in residues in meat from cattle treated with the hormones for growth promotion purposes?

Chairman

779. Dr. Boobis.

Dr. Boobis

780. My view would be that, given the information that was available, it would have been possible to conclude that there was no evidence that at the levels present in meat these compounds would represent a risk of cancer in individuals so exposed.

Chairman

781. Thank you. Any other comments? EC.

European Communities

782. Chairman, I would not like to ask a question now, but would I have the chance to cover this point later on, if you allow me, so that I give the chance to the Canadian delegation to continue?

Chairman

783. If it is a one-time question then I would give the floor to the EC delegation now, but if you have to continue on then I will come back later.

European Communities

784. Well, I think we would like to ask Dr. Boobis and eventually the other scientists to clarify what kind of risk we are talking about. Is it the same as we were talking before, no appreciable risk, or no risk at all? I don't want necessarily to come to generate all this discussion again, but we argue that here we are not talking about a theoretical risk, we are not talking about zero risk, we are talking about a risk which has not been measured, which is difficult to quantify. This is the point and this is, I think, useful to clarify because there are different legal regimes that we apply for oestradiol and the other five hormones. Thank you.

Chairman

785. Dr. Boobis.

Dr. Boobis

786. In the case of the five hormones and oestradiol, the risk we are talking about is based on a view that there is a threshold for any carcinogenic response and therefore it is possible to apply the

safety-factor approach widely used in the determination of an ADI, and whatever the ADI definition is by whoever wishes to set it, these compounds fall into that category. I will not use the words no appreciable risk because it has been persistently misrepresented.

Chairman

787. Thank you. US.

United States

788. Thank you, Mr. Chairman. I only have a couple more questions. To the experts who evaluated the EC's risk assessment, does the scientific evidence, including epidemiological studies put forward by the EC in its opinion, support the conclusion that other human health risks, such as effects on the immune system, are posed by consumption of residues of these five hormones in meat from cattle treated for growth promotion purposes?

Chairman

789. Before I give the floor to any experts I saw Dr. Guttenplan raising his flag before. I give the floor to Dr. Guttenplan.

Dr. Guttenplan

790. With respect to the five additional hormones, if we said that there is no appreciable risk from oestradiol, then the five other hormones have a much less than appreciable risk, because I see no evidence in whole animal studies that any of those compounds have genotoxic or carcinogenic effects.

Chairman

791. I will give the floor to Dr. Boobis first.

Dr. Boobis

792. Chairman, if there is a follow-up to that, I was going to answer the next question.

Chairman

793. Is Dr. Boisseau going to answer the question now or is it related to the question put forward by the US.

Dr. Boisseau

794. Thank you, Mr. Chairman. I simply wanted to associate myself with what was just said following the question by the Communities, so that there is no need to repeat what Dr. Boobis said concerning the conditions for establishing an ADI threshold. However, there is an additional safety factor which Dr. Wennberg spoke of this morning, I think, namely that the exposure of a consumer to residues is considerably less than the dose that would be acceptable in terms of the ADI. In other words, we must not forget that aside from the safety factor that has been determined and that is used to determine an ADI, there is another safety factor, since the dose, the TMDI, the dose that is in fact ingested, is far lower – somewhere around 4 per cent for oestradiol – than the dose that would be tolerated in terms of the ADI. We must not forget this other safety factor which minimizes the risk, if indeed there is such a risk.

Chairman

795. I am wondering whether there is any other expert who is ready to respond to the US question, not the EC one. US.

United States

796. I would simply reiterate, Mr. Chairman, my other question, Dr. Boisseau and Dr. Guttenplan spoke eloquently to the issue of level of risk. But as to whether the EC has actually produced any scientific evidence that supports a conclusion that any of these five hormones are going to pose other health risks when used for growth promotion purposes in cattle.

Chairman

797. Thank you. Dr. Boobis.

Dr. Boobis

798. I have seen no evidence that from the levels present in meat following the use of the five hormones according to good veterinary practice, that there is a risk to human health.

Chairman

799. Thank you. Any other expert wishes to respond? EC.

European Communities

800. Chairman, I think now is probably the point we would like to make with the diagram, we can make it orally on this precise question, so instead of making it later on, probably you will give us a minute or two to make this question; it relates to this precise point.

Chairman

801. Can I ask the EC delegation to do that in the form of posing questions rather than giving a presentation?

European Communities

802. My name is Frederik Vom Saal and I am a professor of biology at the University of Missouri. I appreciate the opportunity to address the Panel and the experts, and the first issue relates to what was just said, and I would like to ask Dr. Sippell who works with the system a question. We see in animal studies that very small differences – and when I say small in terms of free oestradiol levels 0.05 parts per trillion, that is 0.05 pictograms per ml of oestradiol – are related to differences in prostate size in animals, and it suggests that very small background differences in oestrogen are related to differences between individuals, and we know that individuals have different levels of oestrogen and different response to them, and when we give extra oestrogen to these animals, the amount of response of the animal is greater in the animal with the greatest amount of background level of oestrogen, and that shows that there is in fact no threshold, because the endogenous amount of hormone is already above the threshold and the added amount of hormone in again a phenomenally small amount, below a part per trillion, is detectible against this very small background amount. So I would ask Dr. Sippell whether he really believes that when you are eating meat that has oestrogens in it, is the background level against which it is operating to be considered zero the way it is in a typical risk assessment in calculating an acceptable daily intake, or is the endogenous amount already above threshold and any

amount added to that is just going to add to the risk and the types of effects caused by the endogenous hormone? Is this a question that you can answer?

Chairman

803. Dr. Sippell.

Dr. Sippell

804. It is, of course, difficult to answer such a question as a clinician, but from the experience we have with the low levels, I mentioned this several times before, with the extremely low levels that have been measured by these new recombinant assays, it is conceivable really that this extra burden of oestradiol poses a risk to very small children and particularly prepubertal boys, and this is in line with the very very high sensitivity of prepubertal children to oestrogens induced for other purposes. I mean, lets say, I mentioned the example of Turner girls, whom you treat with really minute amounts of oestradiol.

Ms Orozco

805. I would like to take advantage of your knowledge to pose a question. If such minute amounts of additional oestrogens create an appreciable or more than appreciable risk in your view, why we don't we seem to see effects in prepubertal children or at a later stage in their lives from eating eggs, meat and milk?

Dr. Sippell

806. That's actually an excellent question. One of the important parts of the answer to that is to ask whether there have been changes in human health trends over the past 50 years associated with the beginning of the use of the very large number of different types of estrogenic chemicals that children are now exposed to that they weren't before World War II when most of these chemicals began to be used. And if you look at human health events such as breast cancer and related diseases (for instance, gonadal cancer, genital malformation).

Ms Orozco

807. So that we talk about the same things, I am not talking about chemicals and residues of chemicals, but I am talking about the hormonal component that it is naturally present in food derived from animals.

Dr. Sippell

808. I guess my response to that would be that they are part of a mix of additional chemicals that humans are exposed to now that were not being used 40 years ago, and it is not really possible, for somebody in epidemiology for instance, to state the added risk, the increase in the incidence in breast cancer, in prostate cancer, in obesity – all of the types of things that are related to oestrogen are only associated with one particular source, but each of these sources of oestrogen increase the risk. Each of them independently and they add together, and everything you do to reduce one of those sources of risk reduces the overall risk. So the answer to your question is the evidence from human health trends that practically every oestrogen-related disease has increased, associated with the use of these types of chemicals in products.

Chairman

809. I will give the floor to Dr. Boobis and Dr. Sippell and Dr. Boisseau to respond.

Dr. Boobis

810. Mr. Chairman, just in the interest of clarity I would like to make a brief point, which is that the issue of the effects of endocrine disrupting chemicals found in our environment is one of the most complex and controversial issues in biology today. There is absolutely no clear consensus among scientists; very reputable scientists have different perspectives because the heterogeneity of the data is extreme. There have been a number of international respected reviews which have reported that they could find no direct evidence of harmful effects. I recognize that the absence of evidence is not evidence of absence, which is why I choose my words carefully, but I just wanted to say that we are opening up a very major issue which, as an expert on this group, I have not had the opportunity, nor was I asked, to explore in response to the questions addressed. I would also add that it does not appear to me that the EC used such a consideration in their risk assessment; I can find nowhere reference to some of these papers which were published prior to the EC risk assessment.

Chairman

811. Thank you. Dr. Sippell.

Dr. Sippell

812. In view of the fact that we just lack epidemiological studies in children eating normal meat to be compared with those eating hormone-treated meat, we can at the moment rely only on indirect evidence. And if we talk to our American paediatric endocrinology colleagues, they always report us, and this has been published, that the mean age of start of puberty in girls is lower in the United States – particularly in the not so well-off children, particularly those from black background and Hispanic background – than in Europe. Everybody here in the room knows that the problem of childhood obesity is the highest in the United States on earth, and it is increasing in Europe now, but luckily at a lower rate, and there are some other not so obvious indirect pieces of evidence.

Chairman

813. Thank you. Dr. Boisseau.

Dr. Boisseau

814. Thank you, Mr. Chairman. Just a question for the scientist who spoke for the Communities. He said that there was a trend revealed by an epidemiological study. In his view, is there an actual correlation between this trend and the use of growth hormones in the country of which he was speaking, given that over the past 20 years, although consumption of meat has been steadily increasing, people have been living longer and longer? Is the epidemiological study to which he refers discriminating enough to be able to establish a correlation between the observed effect and the cause?

Chairman

815. EC.

European Communities

816. That's an interesting question. Of course in many epidemiological studies establishing carcinogenic effects is very difficult. But one of the important issues is that associated with the use of these chemicals. There have been very recent trends, such as what was just pointed out by Dr. Sippell – a change in the incidence of puberty which is clearly oestrogen driven, and changes in obesity that have been related to oestrogen. And so associated with the use of these chemicals in beef we do have public-health data that suggest an increase in incidences of abnormalities, and again I agree with Dr. Boobis, the absence of evidence cannot be taken as evidence for the absence of harm, and we have to be careful when studies have not been done to assume that that means that there is no effect. [change of speaker.] Chairman, for the benefit of Dr. Boobis, can I refer him to our risk assessment of 1999, it is on page 20 of our risk assessment, under sections 2.3.2.3, where precisely Professor Vom Saal is cited for his research in the risk assessment, his name appears in the risk assessment, and there is precisely the title of this section is called "The Issue of Dose", and we go through this argument in our risk assessment, so it is not true that we have not included that in our risk assessment, and it goes on for two pages. It is on page 20. Thank you.

Chairman

817. Dr. Boisseau would like to have the floor.

Dr. Boisseau

818. Thank you, Mr. Chairman. Just a quick word on what Dr. Sippell said concerning the clear trend towards obesity among children in the United States. He also pointed out that the situation was getting worse in Europe, in the countries where growth hormones are prohibited and are not used. This brings me back to my question concerning the capacity for discrimination of epidemiological studies, since under two different systems – an American system where growth hormones are used and a European system where they are not used – we note that when it comes to obesity in children there may be a delayed effect in Europe, but the trend is similar.

Chairman

819. Dr. Sippell.

Dr. Sippell

820. But the obesity trend in Europe is at a much much lower rate, so the data from the (US) Centre for Disease Control – I think most of you are familiar with that map of the United States, where year by year the colour is getting darker in almost every state of the United States, in virtually every state. If you compare this with Europe, the rate of progression is much higher (in the USA).

Chairman

821. Before we further proceed, as I mentioned, given the time constraint I may not be able to give you a coffee break during this afternoon's session, but for your information, the snack bar will be open for services for us from 5 to 5.30 so please feel free to get coffees during our conversations. OK. And for your information, three of our experts have to leave this evening by 7 o'clock so I hope we can conclude our discussions by 6, but not beyond 7 o'clock at all. With that I will give the floor to EC.

European Communities

822. Chairman, we have promised to the Panel that we will do our best to finish indeed by the time you have alluded to, but there may be questions we really would like to ask, and you appreciate that this is an important occasion to clarify these issues. If we don't manage by then, what are we going to do?

Chairman

823. So that I hope all the delegations will cooperate with the Panel and experts so that we can complete the discussions before some of the experts leave. Without your full cooperation we cannot finish our business.

United States

824. Shall I continue with questions, Mr. Chairman?

Chairman

825. Please, US, go ahead.

United States

826. I only have one more question, actually, to keep things short, and it was interesting that there was a long debate on oestradiol when the question I asked was about the five provisionally banned hormones, and they are not involved in this debate whatsoever. To the experts who have opined on this issue, do any of the scientific materials presented by the EC in its opinions support the conclusion that bovine ears containing hormone implants enter the human food supply in the United States? If so, what is this evidence?

Chairman

827. Can I ask any of the experts to respond. There seems to be none

European Communities

828. Is it part of any of our areas of expertise to be able to trace what happens to bovine ears in the United States. I mean it is not in my area of expertise.

United States

829. Perhaps I can clarify it, Mr. Chairman. The EC in its 1999 opinion has a section under its misuse section that claims there is a risk from implants in bovine ears being processed into the human food supply, and I am wondering if the experts are aware of any evidence put forward in that Opinion that supports that hypothetical situation?

Chairman

830. No experts ready to respond. Dr. Boobis.

Dr. Boobis

831. I could find no direct evidence for such an occurrence. I found studies which explored the implications should it occur, but I could find no direct study of such an occurrence. I am not an expert and I could not say how this would be done, but in reading the literature provided, the materials provided, I could not find a specific study in which that had been investigated with the results presented.

Chairman

832. Thank you. EC.

European Communities

833. Chairman, probably the scientists have not understood, and if you allow me I would like to come in on this point because I think that it is an important point. We have submitted a number of Exhibits to the Panel and they are also mentioned in our risk assessment. The point is whether there are estimations or not how sure are we today that good veterinary practice is always respected in the United States, and in the evidence we have provided there are instances where good veterinary practice has not been observed. We have done specific inspections in the United States by our veterinarians; they came up with a written report which has been submitted to the United States and Canada, they are aware of this report, that identifies clear instances of the use and misuse, and I can refer to Exhibits 50, 52, 65, 67, 68.

Chairman

834. Is that question posed to the experts or to the US delegation? I am afraid that the experts may not be in a position to respond to that question. Canada.

Canada

835. I don't want to cut off the US questions, if the US has any more questions or any follow-ups. We have a number of questions, with your permission.

Chairman

836. OK. Please go ahead, Canada has the floor.

Canada

837. I think we are going to start with a follow-up on this point. [change of speaker] Yes, Dr. Boisseau in his answer to one of the definitions under the terms and definitions section indicated in describing these hormones that the hormones are implanted in the ear and that the ear is discarded, and the comment of the European Communities on this was that he should have said the ear should be discarded. But I wonder if Dr. Boisseau could give some explanation as to the operating procedures, if you will, in a slaughterhouse that are typically adopted so as to prevent or minimize the extent to which contaminants enter the food chain. And here perhaps not just a reference simply to the ear but to other types of contaminants like faeces, hair, hide, and those sorts of things.

Chairman

838. Thank you. Dr. Boisseau.

Dr. Boisseau

839. Thank you, Mr Chairman. I apologize, but since I am neither a veterinary doctor nor an inspector, I am unable to answer that question. I am terribly sorry.

Chairman

840. Canada.

Canada

841. OK. We have a couple of other questions on a separate issue. [change of speaker] Thank you, Mr. Chair, I have to take us back a little bit in the discussions, my apologies for reverting to an earlier question that came up only indirectly in some of the answers from the experts; it might be important to get some more information on this. In the comments from the experts they referred to homeostatic control or what might be also referred to as balancing systems. Perhaps a few experts could comment on the function of those balancing systems and further describe the implications of these systems for low doses of oestradiol received from meat from treated animals. Thank you.

Chairman

842. Thank you. Any comment? Dr. Boobis, please.

Dr. Boobis

843. Well, as indicated earlier, the endocrine system of which the estrogenic system is part plays a critical role in a number of physiological functions and Dr. Sippell has described some of these very clearly. We have also heard that we are subject to natural oestrogens in our diet and we have been for a long time. We have also heard that oestradiol levels can vary or fluctuate, and because of the criticality of the signalling system, it is important that the body is able to balance the levels of oestradiol against that required to produce the responses necessary. And so in general terms there is a system of checks and balances where the turnover of the hormone – any excess hormone tends to be balanced out to some extent. That is part of the role of the binding hormones, sex hormone binding globulin SHBG, it binds a large percentage of the free oestradiol in the circulation normally. And so the homeostasis is a way of preventing extraneous sources from completely unbalancing a tightly regulated system. That is just a general description, I am not saying that that is always the case under all circumstances at all life stages, but that is a general description of the homeostatic regulation of these systems.

Chairman

844. Thank you. Dr. Sippell.

Dr. Sippell

845. I only agree, but there are instances and reports, of course case reports, not epidemiological studies, that for instance children who are exposed to oestrogen-containing ointments, for example, which are being wrongly prescribed, and I have observed personally such cases, young girls get breast development and get a growth spurt and have changes in their behaviour and after this effect has been detected and the cause of that effect has been stopped, then, because the body and the hypothalamus of course react to the withdrawal of this exogenous source very sensibly, then this young girl enters into central precocious puberty, which then creates another problem. So precocious pseudo puberty caused by oestrogens from outside, if this is being stopped then the body reacts with central

precocious puberty, and this to our understanding might be the underlying mechanism why chronic low-dose oestrogen exposure to prepubertal children might result in an early onset of puberty. And, just to give you another example, several other observations have been made with DDT exposure in young children that have been adopted (from the Third World) to European countries, and in them also a high incidence of precocious-central puberty has been observed, after withdrawal of this exogenous oestrogenic compound.

Chairman

846. Dr. Boobis and then to Dr. Guttenplan.

Dr. Boobis

847. I just wanted to make a comment, Chairman, about the observational studies suggesting changes in, for example, the instance of precocious puberty and how that might be associated with the levels of hormones in meat. But as any epidemiologist would be happy to explain, there is a serious danger in trying to compare disease trends in two different countries because of the substantial differences that can exist. It is always possible to point to one factor and say it might be responsible, and of course it might be, we cannot say, but that is one of the reasons that in a risk assessment we tend to base our conclusions on evidence and not on speculation. And in the case, for example, of US versus Europe, we can all point to very many differences, any number of which can explain differences in disease trends, and it's impossible to say that it is due to levels of the hormone, and in fact it is less likely to be due to that than to some other clearly discernable differences between those populations. And on the homeostatic question, I would just add this is very much a question of dose. Toxicity or adverse effect is sometimes described as the breaking of homeostasis, you exceed the level within which the body is able to compensate by homeostatic regulation and then you begin to generate adverse effects.

Chairman

848. Dr. Sippell.

Dr. Sippell

849. Very briefly. If I understand the literature correctly all these homeostatic experiments have been derived from adult individuals, and not from prepubertal or very young children, and I wonder whether these mechanisms are the same in the young child as they are in the adult. And you just said, those case reports have been put together by speculation, this is really not the case, the levels have been measured in these individuals, in these patients, because they are patients and we are allowed to measure at least in them.

Chairman

850. With the understanding of Dr. Guttenplan, may I give the floor to Dr. Boobis to respond first.

Dr. Boobis

851. I certainly did not suggest that the case reports were speculation. I am talking about the differences in trends between the US and Europe, and that the linkage is the growth hormones in meat. That is speculation because we have no evidence for that. It might be biologically plausible speculation to some, but it is speculation; there is no direct evidence for that.

Chairman

852. Thank you. Dr. Guttenplan please.

Dr. Guttenplan

853. I actually was going to respond to the homeostatic question, but just to comment on Dr. Boobis's last comment. Maybe it is not speculation, but often, the term that's used is it's consistent with. So yes, the trends, the time trends in different countries are consistent with the effect of oestrogens, but they are consistent with a lot of other trends too. So I would not say it's speculation, but on the other hand there is certainly no direct evidence that one particular component is responsible for a time trend in oestrogenic or prepubertal effects. With respect to the homeostatic control, at least in experimental animals it's very easy to exceed that. There have been many studies published on animals where oestrogens were administered by all different routes, and you get oestrogenic effects. So homeostatic mechanisms act, but they are not 100 per cent effective.

Chairman

854. EC.

European Communities

855. Chairman, on this point, I think it was a very useful clarification by Dr. Guttenplan. So do I understand correctly then, when you say it is consistent with, that means it is one possible explanation why we observe it. We cannot say this is the only one, but it can be one of the explanations why. That is your statement?

Dr. Guttenplan

856. That is correct.

European Communities

857. Thank you.

Chairman

858. Thank you. I am sorry, sometimes I don't notice the flag of the Canadian delegation. I give the floor to Canada now.

Canada

859. Thank you. We don't usually tend to be as noisy as some of our friends. I just wanted to ask a point of clarification. First of all I should say that in the Canadian diplomatic service Brussels is usually known as a 10 kilogram posting; that is to say that in the first year on average everyone who gets posted there adds about 10 kilos. I am not sure that this is anything to do with levels of hormones in Belgian beef, but it may have something to do with the levels of butter. The question I had was with respect to Dr. Sippell's instances and reports; I understand that he mentioned something about children who are exposed to oestrogen-containing ointments, and I'm far from being an expert in this area or indeed even remotely close to being a scientist, but I gather that ointments are a different means of getting a particular drug into your system than eating something, considering that there is, well, the intestinal tract that about 9 meters long and things happen to it in a different way than when you put an ointment on. So I wonder about the relevance of that, and the other thing of course is that I

go back to what Dr. Boobis mentioned and Ms Orozco, that these oestrogens or oestrogen-like compounds can be found in many green plants. I mean is there any observation, any instance of a boy turning into a girl as a result of eating too much broccoli? You know, that is the kind of information that perhaps we are lacking. But my specific question was to Dr. Sippell in respect of the ointment. Is there not a difference between ointments and taking something orally?

Dr. Sippell

860. May I answer to that very briefly. Oestradiol-17β is a highly lipophilic substance which means that it is being absorbed almost 100 per cent by an infant's skin, more than by the intestinal tract. And this is long known to paediatricians and to endocrinologists, and as a matter of fact for instance testosterone replacement in adult men now is being done by topical gels and creams and ointments.

Canada

861. Thank you, Dr. Sippell, you have made exactly the point I wanted to make. Thank you.

Chairman

862. Thank you. Does this exhaust the list of questions from Canada?

Canada

863. In light of the discussion about consistent with and relationships between a consumption of hormone residues in meat from treated animals and the early-on set of puberty, if I recall correctly there was some mention of the fact that the incidence of early puberty in females of African-American descent was higher than in other sub-populations, and my question is: is there any evidence to suggest that this sub-population consumes more hormone-treated meat than other sub-populations? And if the evidence was that they didn't consume more, that they consumed on average the same, then would that not be evidence that the exposure to hormone-treated beef is consistent with a conclusion that it has no impact whatsoever on the early onset of puberty, because the early onset of puberty is occurring for other reasons?

Chairman

864. Dr. Sippell.

Dr. Sippell

865. Unfortunately there are no epidemiological data to prove or to discard this very question, but there is indirect evidence. There has just been a new study in Germany where they compared the eating habits of children in different levels of the population, high-income, middle-income, low-income families, and they found out that children from low-income families consumed considerably more junk food, so-to-speak, and also higher amounts than an average-income-family child or a high-income-family child. For instance because they don't even have a common meal at home. Unfortunately we don't have such scientifically-sound data, but this might very well relate it with the increasing obesity. And we also know that fat tissues really aromatize, so convert androgens from the adrenals to oestrogens. So those (fat) kids have an additional source of oestrogens entering (from increased adrenal androgens) that turns them into early puberty.

Chairman

866. Dr. Guttenplan.

Dr. Guttenplan

867. Just as I mentioned the term consistent with, I would say studies or at least the statistics among the black and Hispanic community are inconsistent with the hypothesis that oestrogen in beef is responsible for prepubertal and other oestrogenic effects, because I would guess, and I am not sure about this, that consumption of beef by lower socioeconomic status individuals is lower, because beef is expensive. If you look at what is ordered at McDonalds, it is French fries and Coca Cola.

Chairman

868. Thank you. Our discussion is going too far beyond the issues of our constitution here, the focus of our discussions is whether or not the scientific evidence is sufficient in terms of risk assessment of hormone-treated beef consumption. So I think in order to focus our discussion on the subject at hand, I hope the delegations and parties and experts may not go beyond this range of discussions here.

Ms Orozco

869. Mr. Chairman, in order to bring back the discussion to the problem that we need to solve, I would like to come back to a question that was raised, I think, by the United States some moments ago, and I would like to ask the experts if they can please one by one express opinions, because the time is running and you will go away and we will have to decide, and we need your best judgements. With respect to the five hormones, progesterone, testosterone, trenbolone, zeranol and melengestrol acetate, was the existing evidence, the existing scientific information sufficient to complete the risk assessment? We started to answer that question, and I would like to go back to that question, and in those cases where you think the information was not enough, if you can identify what in your view would be missing, or if the information would be enough to complete the risk assessment. I think Dr. Cogliano was answering and was explaining that it depends on what type of risk assessment. The type of risk assessment that we have in mind is the completion of four steps that are common to risk assessments nowadays. So I would really appreciate if we can go back and try to address those two points of that question.

Chairman

870. The floor is open. Dr. Cogliano.

Dr. Cogliano

871. I would say that if you are going to do a JECFA-style ADI, the data are sufficient to do all four steps of the risk assessment. If you wanted to do a low-dose prediction of risk at levels you might find in hormone-treated meat, the data are not sufficient because you cannot estimate that dose-response curve with any kind of certainty. I think I would like to get away from the idea "is something sufficient to show a risk from a particular kind of low-dose exposure", because I think in many cases, in industrial chemicals for example, we get data from occupational studies or from high-dose experimental studies, we conclude that a risk is possible at lower doses and we take action without asking the question – do we have evidence that eating fish from the Hudson river is going to increase your burden of something? People don't often do studies at very low levels; we know what we know about hormones often from high-dose studies in animals, or from large studies in human populations, generally of people who have taken higher doses. I think that I see a disconnect in the

way the scientists like to talk about something and the way the lawyers can phrase questions, because I can answer that, no, the data do not demonstrate that there is a risk from consuming hormone-treated meat. I can also say, yes, the data are consistent with the possible risk, and I think it is the way these questions are phrased. I go back to your question about: are the data sufficient to do a risk assessment? If I were to assume a threshold exists, the data are sufficient to do the kind of – take a no-effect level and divide it by 100 or 1,000. If I were not to assume a threshold, the data are not sufficient for me to describe the low-dose risk and to predict whether it is one in a billion or one in 5 trillion; what the risk is from eating hormone-treated meat, because I cannot estimate that dose-response curve. That's more the way I would think about it: in the language of science rather than phrasing a question to elicit a yes answer or a no answer.

Chairman

872. Dr. Boobis.

Dr. Boobis

873. In my opinion there are sufficient data on all of these hormones to perform a risk assessment and the data support it. In deterministic risk assessment, which means there is no requirement to extrapolate to very low levels of exposure, we can establish an ADI and compare this with the estimated human exposure, and when this was done, the exposure, as you heard from the JECFA secretariat, is only a tiny fraction of that ADI, and so the risk assessment was possible.

Chairman

874. Thank you. Dr. De Brabander.

Dr. De Brabander

875. Yes, Mr. Chairman, I was a little bit, more than a little bit, surprised about the question put by the United States about the implants in the ear. If implants in the ear should enter the food chain, that should not be very well, I think. But it was linked to good veterinary practice and the application of good veterinary practice, and there was put in evidence, and I cite EC-12 here, that meat which was imported from a hormone-free programme in the United States and analysed in European labs still contains hormones, first, and secondly contains hormones which were not allowed for the type of animal. Those are facts. So I would ask – I am not in a position to ask questions to you, I think, Mr. Chairman – you could ask, if there are such findings in an hormone-free programme, what should be the findings in a not hormone-free programme? And that is the question. All we heard from JECFA is all the data we are talking about, I won't go into risk assessment because I am not a specialists in it, but it always said it has to be according to good veterinary practice, and here clearly shown from data, from evidence, that even in an hormone-free programme good veterinary practice is not followed. So can we be sure that good veterinary practice is followed in a not hormone-free programme? And as I answered, there are more products that can be used for growth-promotion than just hormones, and it can add an effect above the hormones. And if there is no monitoring for them, how can you be sure that they are not being used and that good veterinary practice is used?

Chairman

876. On this point? Thank you.

European Communities

877. Well, I would like to ask, because it is part of the evidence. Dr. De Brabander, if hormones, for example in the United States – we know they are sold over the counter. Really, is that good veterinary practice in your view?

Dr. De Brabander

878. In my view not. Normally in Europe we have a very strict regulation and that is one of our problems in the laboratories, that it practically causes a lot of paperwork for us to have just a standard for analyzing samples. If we would have all the standards, 20 milligrams, 10 milligrams of them, which would not be enough to anabolize a fly or mouse or something alike and it can just be used for analytical purposes. We have to fill in piles of papers and in other places they are sold freely.

Chairman

879. Thank you. Do you want the floor now?

United States

880. I don't want to get in the way of Madam Orozco's question -- this is sort of a distraction from that. The United States looks forward to speaking of these issues probably on Monday, when we get into the evidence that has been provided here today. I would make two comments though, one of which was the United States question whether implants in ears had found their way into the food chain. This is a conclusion, a scenario that the EC's 1999 opinion postulates. There simply is no evidence of that. There is nothing there in the Opinion that demonstrates this conclusion. Now if occasional situations where the US hormone-free programme had incidences of meat that was outside of normal ranges, the United States, we feel, and as we are ready to discuss on Monday, has a very robust system, and finding problems, addressing problems, and taking care of them within a regulatory structure, I think, is the utmost attempt to achieve good veterinary practice, rather than evidence against achieving good veterinary practice. And again I look forward to going into that in great detail. I would note that on the other hand the EC, which has chosen to ban these materials, has a well-documented black market for their use per the Stephany paper that the United States has presented. So, when we talk about failure of good veterinary practice, I think this is a fairly complex discussion that maybe these most recent comments oversimplified a little bit.

Chairman

881. I will give the floor to Canada.

Canada

882. Yes, I would like to ask a follow-up question to Dr. De Brabander's comments, and that is: are you familiar with the Canadian Food Inspection Agency National Chemical Residue Monitoring Programme, and have you had an opportunity to review the results of that Programme for, let's say, the last five years?

Dr. De Brabander

883. No, I'm not, that is simple. I am a chemist, I am working in a lab, involved in routine control, I'm not inspector, a veterinary inspector, and not a European inspector, but there are.

Canada

884. So you don't have any expertise to share with this Panel as to the control mechanisms in place in Canada to minimize or to prevent misuse and abuse of these hormones.

United States

885. We will just follow-up, Mr. Chairman, and ask the same question of the US system of controls.

Dr. De Brabander

886. I think the question is beyond our role as an expert. As an expert we have been asked to examine the papers, and my role is not going inspecting in the United States, neither in Canada. But evidence is here. I was involved in problems with the import of American pork meat. I was asked by the USDA to perform some analysis and some studies on that phenomenon, from which there was evidence from urine that also pork should be treated with hormones. That I have practical experiences in.

Chairman

887. I think Canada has been interrupted so many times while you were posing questions; I am wondering whether Canada has exhausted its list of questions.

Canada

888. We just have one more question on detection methods of residues and perhaps we can ask this question. I think this question follows on one of the Panel's question and it was answered by both Dr. De Brabander and Dr. Boisseau. And the question is that if you have a Codex MRL, a maximum residue limit that has been adopted by Codex, and you have a detection method that is of a sufficient limit of quantification so as to be able to detect residues at that MRL, so for instance an MRL of 10 micrograms per kilogram, and your detection method has a limit of quantification, about, say, half that, 5 micrograms per kilogram, the fact that you have developed more sophisticated analytical methods that now have a lower limit of quantification, lets say a limit of quantification now of 1 microgram per kilogram, does that mean that the other type of detection method, assuming that it was fit for purpose, that that other detection method is no longer fit for purpose? That's my question.

Dr. De Brabander

889. That goes into very technical details of analysis, technical terms like recovery. What is recovery? Recovery is if you take a piece of meat and you mix it with methanol for example and you add hormones to it, how much do you recover. And that is very dependent upon your analytical technique, and in most cases when you do that your recovery is low, so if you have an MRL of 10 and your recovery is less than 50 per cent, you cannot detect a residue at all. It's that simple. Furthermore, you should be certain that you detect the component in the right form. Certain components may be bound, maybe in another form than you detected. You must be sure that you free them, so it is a question which you can hold a conference on, I think, and maybe I should take a comparison with cars. If you drive at 100 kilometres an hour and you drive it with a car which just is able to get that maximum speed limit you are not comfortable, but if you drive a Ferrari or another racing car who can get up to 220 kilometres, then you drive safely at 100. It's a little bit the same with the analytical technique, if you have an analytical technique that is capable of 1 ppd or 0.5 ppd comfortably, then you can more easily and more correctly measure your MRL. I hope I was clear in that for you.

Chairman

890. Dr. Sippell.

Dr. Sippell

891. And this is just the follow-up to answer your question regarding the situation in children. We just don't have yet everywhere where it would be necessary the methodology, the analytical tools to measure as sensitively as we should do it, and therefore I think that the data available are insufficient. And I also already said before that due to ethical constraints I don't expect that we will get the data we need to answer these questions in the near future.

Chairman

892. Dr. Boisseau.

Dr. Boisseau

893. Thank you, Mr. Chairman. I would like to revert to the question concerning the methods of analysis. I have already answered, but since the question has re-emerged, I'll answer once again. We have to decide what we are talking about. The initial hypothesis was that there was an adequate method to control the established maximum residue limit, i.e. that this method must have been validated. This means, in particular, that the limit of quantification is compatible with the ADI value. I am not speaking of the limit of detection, which is lower, but rather of the limit of quantification. Moreover, this method needs to meet a certain number of criteria defined by the ISO standards such as reliability, reproducibility, precision, linearity in a given range of concentration etc. Assuming this method of analysis has been validated, it must also be practicable. Since any analysis has a cost, it is not necessarily a good idea to choose an ultra-sophisticated method, since what counts is to be able to ensure that the controls are economically reasonable. So if a method meets all of the criteria, there is no point in using a more recent and more sophisticated method. If other laboratories choose to use such methods, that is fine with me, but if a control laboratory is operational and produces good results for the control of that MRL with a method that may be ten years old but that works, I see no reason why it should be changed. The point of the MRL is that it offers the possibility of stopping this rush towards ever-better performance of methods of analysis, since analysts, like scientists, appear to have an infinite capacity to improve, to do more, to be more precise, to be more sensitive, and in general, this means higher and higher costs. Where there is no need, there is no point in investing in that area.

Dr. Boobis

894. I wanted to come back to this question of the sufficiency of information and the correct comments from one of my colleagues that it is highly unlikely we will be able to get information in children of the sort that would be suitable for a risk assessment because of ethical reasons. And this is for oestrogenic or hormonally-active substances. I just want to reflect on the implications of that, because it implies we cannot proceed with a risk assessment without information that cannot be achieved or acquired, and that if we add to that the argument that there is no bottom end to the dose-response curve for oestrogen, and we look at the range of compounds and the range of potencies of hormonally active substances – this is a very diverse and wide-range of materials – does that imply that it is impossible to conduct a risk assessment on any of those materials? I do not believe that is the case. I believe that with a fundamental understanding of biology and appropriate model systems we can make intelligent deductions about the likely risk to the population. That is not to say that there may not be some gaps in scientific knowledge and that there may be severe gaps, but the implication that we can never proceed without information in the target population of children means that we are going to be completely blocked from dealing with these compounds, and these compounds, as I said a

minute ago, are an extraordinarily wide range of compounds, because we have this idea that there is no zero risk for an endocrine-active material.

Chairman

895. Thank you. Dr. Miyagishima first.

Dr. Miyagishima

896. Thank you, Mr. Chairman. I would like to clarify that the terms of reference of Codex on residues of veterinary drugs in foods currently include consideration of methods of sampling and analysis for the determination of veterinary drug residues in foods. And there is a document called Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs. This is not a document which is located in the Codex Alimentarius in a strict sense, but this is a list of methods that are considered to be useful for governments to check that residues in food samples are in compliance with the Codex MRLs. Currently in this compendium there are no methods mentioned for the determination of oestradiol, progesterone or testosterone. This is consistent with the fact that there are no numerical MRLs in place within the Codex Alimentarius. However, this compendium recommends method of analysis for trenbolone acetate and zeranol, for which there exist Codex MRLs, and for melengestrol acetate, for which the draft MRL is currently at step 7 of the Codex elaboration procedure.

Chairman

897. Thank you. Dr. De Brabander.

Dr. De Brabander

898. Just a small clarification, Mr. Chairman, on what Dr. Boisseau said about the MRL. He said that the MRL was installed to stop the race for lower concentrations. Am I correct? And I thought hearing from the JECFA that the MRL was really based on toxicological evidence, it had nothing to do with an analytical technique. I was not aware that they want to stop chemists of doing our work better and better.

Chairman

899. Thank you. No comments from the experts, then I will give the floor to EC.

European Communities

900. Chairman, I would like to take the floor and ask Dr. Boobis – because in his reply to question 64, precisely as he has said, and it is very important in my view to understand, that the level obtained in a residual risk has never been quantified, but is considered to be acceptable to society. So – if I say something wrong, please, Dr. Boobis, correct me – that means he is making a value judgement for himself. He accepts that the residual risk has never been quantified, but he then goes on, every scientist, not a risk manager, every scientist to suggest that this is acceptable to society. And my simple question is: do you think it is a proper position to take of the scientists who are supposed to do a risk assessment in the strict sense? For example this is mentioned in the Codex Manual of Procedure. If I have misinterpreted what you wish to say please clarify it. Thank you.

Dr. Boobis

901. I will clarify. You completely misrepresent what I said and misunderstood my meaning.

European Communities

902. Could you explain then what is the meaning of what you said?

Dr. Boobis

903. Because the risk assessments of JECFA are adopted by Codex, it is implicit that they as risk managers have accepted and established the level of risk that is acceptable for society. This is nothing that JECFA says; it uses a procedure which is acceptable throughout the world, is used by the EU itself to establish ADIs. Implicit in that procedure is therefore the recognition of the level of risk that is represented by that process. It is not my judgement, it is the judgement of risk managers, I am simply interpreting what the risk manager's conclusions must be to allow us to do the risk assessment according to the principles that have been accepted throughout the world. And I stress again, I am not making a value judgement here.

Chairman

904. Thank you. Dr. Boisseau.

Dr. Boisseau

905. Because the question that has been asked is really quite important in terms of principles, I would like to back up what Dr. Boobis has just said. The experts in the JECFA, in particular – but the same applies to the CVMP – do not define a socially acceptable level of risk. They have a working method which uses – within the framework of a deterministic approach – a certain number of safety factors. I note, moreover, that although I made this suggestion yesterday, there was no mention of the chain of safety factors used throughout the procedure up to the determination of the MRLs. There is a whole series of factors, and it is a shame not to bear them in mind, because this would perhaps give us a better idea of the protection provided by the method used by the different scientific committees. Once again, the scientist in charge of risk assessment does not determine beforehand what a socially acceptable risk is, and it is not his job to do so. He makes recommendations on the basis of a methodology which, although not written out, is known to all and used everywhere. At the Codex level, the CCRVDF (the risk management body), fully aware of the method, was perfectly capable of accepting or not accepting the ADIs or the MRLs. We need to distinguish, when it comes to risk management, between those who make the proposals and those who end up deciding. The risk managers are those who decide – they are not the ones who propose. The same is true in other agencies, such as the AFSSA (French Agency for Food Safety), where I worked. As the Agency responsible for assessing all risks connected with food, it often made proposals with respect to management, but it was ultimately the Ministry that decided, and never was the AFSSA criticized for the proposals it may have made in the area of risk management.

Chairman

906. Well, before I give the floor to the delegations, I would like to remind all the delegations that discussions should not escalate to the point of making any offensive remarks in the posing of questions. And I believe that the parties have exhausted their list of questions by now. If that is the case, then I will give the floor to my colleagues in the Panel so that we can also pose questions on area 3, and with that understanding I am wondering whether – the US still wants the floor? OK. Canada has the floor.

Canada

907. Thank you. We just have a couple of more questions for Dr. De Brabander, and this is in relation to your comments that in your opinion there are economic incentives to illegally use

hormones, and I would just like to ask you a few questions on this. At one point in your advice you indicated that hormones can negatively affect behaviour, and my question to you is if you add increasing amounts of hormones to cows, does that increasingly affect their behaviour? And I believe you have mentioned at one point that it makes the cattle more aggressive. So does increasing the amount of hormone increase the level of aggressivity?

Dr. De Brabander

908. I think that is a little bit more than I said, what you take out of my words. I said that hormones may influence behaviour, and there are experiments, not with cattle but with rats, where hormones were added which made them more aggressive. That's right, that's known, that's facts, just facts. I don't know of experiments of a dose-response curve of aggressivity against hormones, and certainly not in cattle. Such experiments we would not do in Europe, not in Belgium, because of ethical reasons. For each animal experiment we have to do we also have to fill in a couple of papers, a number of papers. Luckily at our school we have our own ethical committee, a committee which is controlled, which assesses what experiments must be done, what can be done. I cannot answer your question because it is too far gone, the only thing I said is they really will influence behaviour and that is known in test animals.

Canada

909. Thank you. My question was: if you add more, do you expect to see some sort of a relationship between the effect of behaviour and the amount of hormones, so that if you add more hormones, if you multiply the dose, if you add considerably more hormone than what is recommended, whether this is likely to have an adverse effect on the level of aggression in the animal?

Dr. De Brabander

910. That is too a complex question to answer here on the floor, I think. I think it is a subject for a research programme, and certainly there are people who would like to carry out that programme, but we cannot answer that. I have just said they have an influence on behaviour, that's qualitatively, quantitatively that's not to answer at this moment.

Canada

911. OK. Thank you. I just have another question for Dr. De Brabander. Do you know whether or not the administration of hormones or the overdosing of hormones has an effect on the carcass grade quality – and by that I mean the quality grade of the meat, grade A, US grade A, US double grade A, triple grade A? I take it that the grade is related to the amount of marbling, to the amount of fat distribution, in the carcass. Does administering more hormones than is recommended have an impact on that grade?

Dr. De Brabander

912. Yes. That is also difficult to answer having studied these papers. What I have said is not the addition of more hormones, what I said was there are other components, and I mentioned here zilpaterol, a beta agonist of the third generation which is legal in Mexico, and I mentioned an experiment with zilpaterol I was looking at literature for zilpaterol because we have to monitor it and bring it into line with other beta agonists monitoring programmes. We found out that experiments with zilpaterol were done, and to my surprise the blank animals were not blank animals, but were animals treated with the regular US hormones and they had an extra profit. So if you ask: are there

incentives to use other growth promoters, yes there are, and the same incentives that's the same everywhere in the world: money.

Chairman

913. I think it is our turn, but before I give the floor to my colleague, the floor is for the EC. A quick question.

European Communities

914. Chairman, I would like to say that we have a couple of questions more to ask on this area. I don't know if now is the moment or later.

Chairman

915. Yes, please go ahead.

European Communities

916. Thank you. That question relates to the discussion ... (end of tape) ... concerning the genotoxicity and whether the evidence which we have, which is reported in our risk assessment and subsequent papers which we have submitted, of genotoxicity *in vivo* – because Dr. Boobis has made a statement just before the break saying that in his opinion the evidence is not convincing, I think that is more or less what he has used. So I would like on this precise point, because he made a reference to some papers, to give the floor, with your permission, to one of our scientists to make a short statement and then probably ask a question on this precise point – it's Dr. Metzler. Thank you.

Chairman

917. There is a question to be posed to Dr. Boobis? OK go ahead.

European Communities

918. Thank you, Mr. Chairman. It has been stated that there is not sufficient evidence for the mutagenicity of oestradiol and its metabolites *in vivo*. Before I go into this question, let me just reiterate that we all agree, I think, that, first, the DNA-directed mutagenicity of oestradiol is not due to the oestradiol molecule itself but to one or several of its metabolites which need to be formed. Secondly, these reactive metabolites, which bind to DNA, causing DNA adducts, are weak mutagens, as has been shown in *in vitro* studies. Despite this fact, to my knowledge there are three studies demonstrating *in vivo* mutagenicity of these metabolites and also of oestradiol, one study in mice and two studies in rats. As Dr. Boobis has correctly stated, in most of the studies the metabolite under suspicion for causing mutagenicity has been tested, but in one of the studies in rats, also in addition to this metabolite, E_2, oestradiol itself has been administered to the rat and led to an increased mutation frequency in the mammary gland. So there are three *in vivo* studies on the mutagenicity of oestradiol and its metabolites. And let me just add one little piece of *in vivo* evidence; there is a paper that has demonstrated that the very adducts of reactive oestradiol metabolite that have been shown mutagenic in cell culture studies *in vitro* is present in the human target tissue, the human breast. These adducts have been demonstrated to be there, and this demonstrates, in my view, that even in normal women these adducts are formed, and in my view obviously any additional oestradiol would increase the frequency of these *in vivo* adducts. Thank you.

Chairman

919. Dr. Boisseau – US first.

United States

920. Thank you, Mr. Chairman. I would just make one point. If the experts are going to respond to this, I would hope that they would discuss the levels of hormone that were used in the studies that were just were referred to. I think we may find that the levels used in these studies are exponentially higher or greatly higher than those that are relevant to the subject matter at hand, which is hormone residues in meat, but I leave that to the experts if they are indeed going to respond to this statement. Not to the EC's expert but to …

Chairman

921. Right, thank you, that is clear. I will give the floor to Dr. Boisseau first and then to Dr. Boobis.

Dr. Boisseau

922. Thank you, Mr. Chairman. When we revert to this series of short-term tests to suggest, or conclude, that oestradiol is associated with genotoxicity, potential genotoxicity or mutagenicity, this means that we credit oestradiol with the capacity to induce tumours through a channel other than the hormonal effect. Since the short-term tests are screening tests, these hypotheses, which are perfectly valid with respect to the results of the short-term tests, need to be confirmed through studies on animals, experimental carcinogenicity studies. So this leads me to a question for Dr. Boobis, who is a specialist in this area: have the experimental carcinogenicity tests – 18 months on mice and two years on rats – been able to identify the appearance or increase of tumours in non-hormonally-dependent tissues which are predictive of the same tumours in human beings? In other words, did any tumours appear or develop in non-hormonally dependent organs in animals whose physiological and metabolic characteristics were such that what was taking place in animals was predictive of what could take place in human beings? Thank you Mr. Chairman.

Chairman

923. Thank you. Dr. Boobis.

Dr. Boobis

924. I was just concerned to identify the three studies mentioned by the EC, so that I can look at them. You mentioned three studies that were positive *in vivo*, I would like to know what they were. Thank you.

European Communities

925. May I answer that question? They were cited in EC Exhibit 125, so they have been provided.

Dr. Boobis

926. Authors of those papers, to help me find them?

European Communities

927. The first author is Cavalieri, and I think Professor Guttenplan is also on the author list. I am sorry, there are a number of authors and I cannot remember all of them but there are seven or ...

Chairman

928. Dr. Boobis, do you need some time? Dr. Boobis, I think the secretariat may provide you with the relevant materials. OK. So in the meantime, can I give the floor to the EC to respond to the question put forward by Dr. Boisseau? Dr. Boisseau please.

Dr. Boisseau

929. Excuse me, Mr. Chairman. I had directed my question to Dr. Boobis, and not to the Communities.

Chairman

930. Thank you.

Dr. Boobis

931. Chairman, what I have in front of me at the moment is EC 125, an unpublished review. Is that correct?

European Communities

932. The draft you have is the prepublication available for the internet and it has been published and it has appeared in the meantime, in August 2006.

Chairman

933. Thank you.

European Communities

934. It's a review and it contains also original data on later pages.

Chairman

935. Please go ahead, Dr. Boobis.

Dr. Boobis

936. I have not had time to evaluate these date. This is a recent review, I hear that it came out less than six weeks ago, I have not been in my office for much of that time, I have not had time to read this paper. If possible I will look at it and maybe be able to have a comment in the next half hour.

Chairman

937. Thank you very much. I would appreciate it if you could do so. Does the EC want the floor?

European Communities

938. I think we are satisfied with the reply and we would appreciate it if there is a reply later on. Thank you.

Dr. Boisseau

939. Thank you, Mr. Chairman. Without wishing to harass Dr. Boobis, could I ask him please to answer the question that I directed to him – or perhaps he did not hear it; he may have been looking at the documents that he had just received from the Communities.

Chairman

940. Before I give the floor – Canada has the floor.

Canada

941. My apologies for interrupting the flow of discussions. It is simply a point of clarification. My colleagues tell me that the document as published may well be slightly different or different in certain key aspects, however way one looks at it, from the documents as a draft that has been put in evidence. So I just want to confirm whether in fact those who are familiar with the published version can guarantee to us, talking about appreciable risk, if they can guarantee to us that the document as published is in fact the one that we have in our possession, or alternatively what the differences are. We would like to know if in fact the reference made is to the published article or to the draft article. You will forgive the confusion here, but I think a better precision is probably useful, and we don't want Dr. Boobis to review a document that in fact may not be the document to which reference is being made.

Chairman

942. I think regarding that question we can benefit from the response or comments by Dr. Guttenplan, because he was one of the co-authors. We can ask Dr. Guttenplan to clarify on that point later maybe. Is the US point also related to this one?

United States

943. Simply to say that I was going to try to assist Dr. Boobis in his search. I think a relevant section to look at is section 5.2.1 in that study. There are a couple of paragraphs there that might shed some light on the methodology and how it actually relates to this dispute. That assumes I am looking at the unpublished version that – oh I am looking at a published version, I am not sure which version the EC's Exhibit is.

Chairman

944. EC has the floor.

European Communities

945. Chairman, if you see with our comments on the comments of the parties which we have sent on 12 July, it is all these papers cited by Dr. Boisseau, Dr. Metzler, they are cited there in our comments to question 13. So this has already been sent to the Panel, and the other papers as well, at least on 12 July when we submitted these papers. You will see them clearly cited, all the three papers have been mentioned. Thank you.

Chairman

946. Thank you for that clarification. I am afraid that Dr. Guttenplan was out of the meeting room for around ten minutes, so I am wondering whether he has followed the discussions so far?

Dr. Guttenplan

947. No, I haven't.

Chairman

948. Maybe the EC can briefly explain what he mentioned again.

European Communities

949. Well I can answer that question, I think, if I understood correctly. What has been submitted in May or June or in July was the pre-publication, and the pre-publication means it is not a draft, but it's the final paper that appears on the internet, because the Journal where it is published usually appears two or three months later. So it is identical and it has appeared in the Journal now in August and I would be happy give you the reference, which is volume 1766, pages 63 to 78, Biochem. Biophys. Acta., as is already on the pre-publication.

Chairman

950. So, until we reach the time when Dr. Boobis is ready to respond to that particular point, shall we move on to the next item on EC's risk assessment? If we have wound up the discussions on area 3, I will give the floor to the EC first to put questions on section 4. EC has the floor.

European Communities

951. Chairman. With your permission, while Dr. Guttenplan was away, I think a member of the Panel, Madam Orozco, has posed the question on the sufficiency of the evidence, and I think practically all the scientists have replied, I thought, except Dr. Guttenplan, if I am not mistaken. So could you please make sure that we have the views of all the experts on this issue, and probably, if I may suggest, that Madam Orozco repeats the question again if possible. Thank you.

Ms Orozco

952. Yes, Mr. Chairman and the experts who are assisting the Panel, I posed a question and I would appreciate answers as complete as possible, because we have a situation where the European Communities has stated that in their view they did not have sufficient evidence, sufficient information, to be able to carry out a full risk assessment on the five hormones other than oestradiol-17β. I have posed the question and I have asked your views as to whether or not the information that is available is sufficient to carry out the four-step risk assessment that we are talking about.

Dr. Guttenplan

953. These are the five hormones in addition to oestradiol? I don't know about a full risk assessment, but I think there is enough data to carry out a risk assessment as Dr. Cogliano refers to.

Ms Orozco

954. Because the terms are not always used in the same sense, what we are talking about is the four steps of a risk assessment, or a risk assessment that for some good reason does not have them, but in principle we are talking about a risk assessment that would have a hazard identification, that would have a hazard characterization, that would have an exposure assessment and that would have a risk characterization step. Whether or not the information that is available would be enough. If not, what is it in your view that is missing to be able to carry out a full risk assessment?

Dr. Guttenplan

955. I think there is sufficient information out there.

Chairman

956. Thank you. Dr. Boisseau.

Dr. Boisseau

957. I am going to answer along the same lines as Dr. Guttenplan, in that the method usually applied by the JECFA is considered satisfactory because it is a deterministic method. Now, if we are talking about a probabilistic method with effect–dose extrapolation to low doses, the data may not be sufficient. Consequently, my reply to Mrs Orozco's question is that my answer depends on the method applied by the JECFA.

Chairman

958. Thank you. Dr. Boobis.

Dr. Boobis

959. I have a comment on one of the studies that were referred to recently. Would you be prepared to listen to that now? A comment on one of the genotoxicity studies that were referred to a moment ago. This is an *in vivo* study of oestradiol. I note that it was a high dose – it was toxic – and that the mutational spectrum, which is a very important measure of the underlying mechanism whereby the interaction with DNA was occurring, was not significantly different from the control animals, and that the 4-hydroxy-oestradiol, which was the presumed metabolite, as Dr. Metzler has just pointed out – a possibility that the parent is not itself responsible but a metabolite – had a quite different mutational spectrum. So my view would be that this study is not sufficient at the present time to override the conclusions that we had come to earlier, that low doses of oestradiol do no cause a mutagenic response *in vivo*.

Chairman

960. Thank you. Dr. Guttenplan please.

Dr. Guttenplan

961. The mutational spectrum for 4-hydroxy-oestradiol was different in the control.

Dr. Boobis

962. I stipulated that the mutational spectrum for 4-hydroxy-oestradiol was different from the control, but that of oestradiol was not, and if the hypothesis was that the effect of oestradiol in producing that response is through the 4-hydroxy metabolite, the anticipation would be that there would not be a very big difference in the mutational spectrum; there was.

Dr. Guttenplan

963. Well, we don't know how much of the oestradiol gets converted to the 4-hydroxyoestradiol, and it has been detected *in vivo*, or at least the conjugates have, in breast tissue from human women, and we know that that gives a different mutational spectrum than the control.

Chairman

964. Thank you.

Dr. Boobis

965. Could I just respond, please? But the problem I am having, Chairman, is that the compound we are concerned about is oestradiol. I can find no difference in the mutational spectrum, which is a signature of the response to the DNA, from the control. So it may be exaggerating something that is going on naturally, and I would repeat that the dose of oestradiol used in these studies was so toxic that not all the animals actually survived.

Dr. Guttenplan

966. Yes, this is a common problem with any toxicological study, you have to increase the dose in order to see something that is significant in the animals, you don't have enough animals to do the experiment if you were to use an environmental dose. So this is nothing different than what is done in usual toxicological studies.

Dr. Boobis

967. There have been guidelines established for dose setting in studies in which mutational responses have been observed *in vivo.* I do not believe that any of those guidelines recommend going up to doses which are lethal. There is supposed to be some slight evidence of toxicity at the top dose, but by no means lethality, so this would be a heroic study.

Dr. Guttenplan

968. 4-Hydroxyoestradiol was not toxic though, just oestradiol alone, and often this is what you do, you test the presumed active metabolite. And this is often done, this is classical studies in metabolism of benzpyrene, as you are familiar, which were eventually done with the end product.

Chairman

969. One last chance for Dr. Boobis.

Dr. Boobis

970. I agree entirely with what was just said. In the case against benzpyrene, however, the parent compound and the metabolite produced the same mutational spectrum, therefore confirming the likely

involvement of the metabolite in the response. Here, when we see a different mutational spectrum, the interpretation for me is: something else is going on; and it certainly does not confirm, it by no means confirms, the involvement of that metabolite. It may be that there was too low a level, but these data cannot be used to confirm that metabolite's involvement in response to the parent compound. That's all I was saying.

Chairman

971. Well, we have spent more than two hours already and we still have the most important issue of our consideration this afternoon, so I think it is better for us to move on to the next section on the EC's risk assessment, and then I will give the floor to the EC first to ask questions to the experts. You have the floor, EC.

European Communities

972. One question I would like to ask the experts, and in particular probably Dr. Guttenplan or Dr. Boisseau, is that, as we know these substances, the implants contain several of these hormones that, as we were told, they practically never are administered as a single substance, and Dr. Boisseau in his reply has confirmed that. The toxicological evaluation was made on an individual substance. Now how important do you think it is to know the possible synergistic effects, given that the actual administration of these implants involves more than one of these hormones? Thank you.

Chairman

973. Thank you. Dr. Guttenplan.

Dr. Guttenplan

974. I think that the biological effects of oestradiol so overwhelm the other effects that I would not be concerned with any synergistic effects.

Chairman

975. Is any other expert prepared to respond? If none, the EC has the floor.

European Communities

976. Chairman, it is not entirely clear how the current section differs from the previous one. In your instructions, your indications, you said section (c) and part of section (d), so I would like to discuss a specific aspect of the EC risk assessment which was discussed under the previous section. If you allow me to ask a question to Dr. Guttenplan.

Chairman

977. Sure. There is no clear-cut dividing line between these two areas. You can put whatever questions you feel are necessary.

European Communities

978. Thank you. It is just that, if I understood correctly, Dr. Guttenplan, you said that the scientific evidence on the five hormones was sufficient to conduct a risk assessment. In your reply to questions 61 and 62 you actually state differently, so could you explain the differences? There is a whole

bullet-point list of gaps you have identified, and in your reply to question 61 you speak of an assessment for melengestrol acetate which seems sound for example. Could you explain?

Dr. Guttenplan

979. That means that the risk assessment was alright.

European Communities

980. Would you care to elaborate on the gaps you have identified and question 62?

Dr. Guttenplan

981. Yes, on subsequent reading I could not find anything to indicate adverse effects, and I now think that risk assessment is alright.

European Communities

982. Can I reformulate the question? Because I think probably we have an issue of understanding each other. Can I ask, Dr. Guttenplan, whether your reply to question 61 is correct as you see it today?

Dr. Guttenplan

983. Well, I said the ability varies between compounds, but that does not mean you can't make a risk assessment, it just means the accuracy of the risk assessment is different.

European Communities

984. You also say, for example, that it does not appear that accurate ADIs can be established at this point.

Dr. Guttenplan

985. Well accurate means – if it's not accurate, there is just a larger range, but you can still do a risk assessment.

Chairman

986. I will give the floor to the US.

United States

987. Thank you, Mr. Chairman. Dr. Guttenplan actually spoke to our question, which was whether these particular items he had identified in this question actually prevented the conduct of a risk assessment, which is entirely separate from whether there are certain small gaps, whether you can actually conduct a proper risk assessment.

Chairman

988. EC, please, go ahead.

European Communities

989. Chairman, we have asked previously a question about the fact that the hormones are administered in combinations containing more of these hormones, and only Dr. Guttenplan has replied. Probably Dr. Boisseau would like to give a reply. Would it be necessary to have an assessment that takes into account the real administration of these hormones and not the individual compounds in question?

Chairman

990. Dr. Boisseau, please.

Dr. Boisseau

991. The same type of study was conducted for trenbolone, which, if I recall, is administered jointly with oestradiol, and no particular potentiation effects emerged. These studies of combinations of hormones were not conducted for all hormones. The JECFA considered that since the receptors were not the same and the biological properties were not the same, the prospects of a hormonal potentiation effect through the action of another hormone was unlikely. So if I am not mistaken, toxicological studies were made only for trenbolone. That is all I can say.

Chairman

992. Thank you. I would like to thank Dr. Wennberg and Dr. Miyagishima for their contributions and presence in this meeting. I would like to let the delegations know that they are leaving. Thank you. The floor is for the EC again.

European Communities

993. Chairman, I would not ask a question now; we will wait for the other part before we intervene.

Chairman

994. OK, good news. US has the floor.

United States

995. Thank you, Mr. Chairman. A question for all of the experts who have looked at the EC's risk assessment and have comprehension of the four steps of risk assessment; hazard identification, hazard characterization, exposure assessment and risk characterization. In light of these components, have you identified any deficiencies in the EC's opinion relating to oestradiol-17β?

Chairman

996. Thank you. Any volunteers? Dr. Boobis.

Dr. Boobis

997. Well, in looking at the four stages of risk assessment, as we have heard earlier, for various reasons the EC evaluation tended to focus more on the hazard identification side. There was some hazards characterization but it was not completed and, as far as I could gather, there was no

independent exposure assessments undertaken. And so, from the perspective of the four stages, it would certainly not be regarded as a complete risk assessment.

Chairman

998. Dr. Boisseau?

Dr. Boisseau

999. I concur with Dr. Boobis.

Chairman

1000. Thank you. EC?

European Communities

1001. Can we follow up on this? Dr. Boobis, is your reply based on the assumption that there would be a threshold, so that your reply would actually not apply in the case of direct genotoxicity?

Dr. Boobis

1002. That is partially correct, but I would have anticipated some exploration of the type of genotoxicity and whether it did have a threshold, and that does not seem to have been carried out very rigorously and there was not what I call the weight of evidence, a sort of balancing of the quality of the studies and the endpoints that they were responding to.

Chairman

1003. Dr. Boisseau.

Dr. Boisseau

1004. Thank you, Mr. Chairman. We always seem to come back to the problem of thresholds. Once again, short-term tests that can show a genotoxic or mutagenic potential are not intended for determining thresholds. If we really want to know whether this potential is real, it needs to be confirmed by long-term carcinogenicity tests. So I come back to my question to Dr. Boobis: in the long-term tests on mice and rats, was it possible to identify tumours in non-hormonally dependent organs that could confirm a mutagenic potential observed in short-term tests, and if so are such tumours in non-hormonally dependent animal organs predictive of what could happen in human beings?

Chairman

1005. Thank you. Dr. Boobis.

Dr. Boobis

1006. Apologies, Chairman, I did not catch that question to respond to earlier. From my knowledge, the studies in rodents have not shown any target tissues for carcinogenicity which are not hormonally dependent and that these tissues are targets one would have anticipated for an oestrogenically active substance. That is the factual evidence.

Chairman

1007. Do these answer the question by the US?

United States

1008. Yes, Mr. Chairman, thank you.

Chairman

1009. No further questions from the US? What about Canada?

Canada

1010. No further questions from Canada.

Chairman

1011. Thank you. I give the floor to the EC.

European Communities

1012. Thank you, Chair. On this last reply of Dr. Boobis we would like to intervene, and I would like to give the floor to Dr. Alain Paris who would like to respond to this please. [Change of speaker.] Out of courtesy towards Dr. Boisseau, I am going to speak in French. I am surprised at the division that has appeared, with regard to the action of oestrogens and their effects, between what passes through the oestrogen receptors and what passes via genotoxicity phenomena. To revert to the genotoxicity phenomenon, this is essentially a random process; and I wonder about the deterministic approach, as mentioned earlier, which would appear to be more efficient than the probabilistic approach, in that the deterministic approach, in my opinion, is incapable of taking account of all of these random phenomena.

Chairman

1013. Thank you. Dr. Boisseau.

Dr. Boisseau

1014. Thank you, Mr. Chairman. I am no specialist in these areas, but reverting to what you said, and I agree with you, a phenomenon based on genotoxicity or mutogenicity is random, which means that this genotoxic potential, if it exists, should, in a carcinogenicity study, provoke tumours which should concern a certain number of tissues in a random manner and not only those which are hormonally dependent. Hence my question earlier on, which was answered. For the moment, the only tissues affected by the development of tumours are hormonally dependent. This does not support the idea of a non-hormonal genotoxic-type mechanism. Finally, the statistical evaluation of the effect of small doses is another problem.

Chairman

1015. Thank you. Dr. Guttenplan please.

Dr. Guttenplan

1016. The genotoxic effects, at least the mutagenic effects, are also dependent on cell proliferation, and sometimes they are extremely dependent on cell proliferation, so that hormonally-sensitive tissues in the event of a random distribution of a genotoxic effect are going to show the first genotoxic effects. So it is not surprising that you see effects in animals in hormonal-sensitive tissues. Of course one could make the same arguments for a non-hormonal mechanism, too. On the other hand, one could make the same argument on a hormonal model as a genotoxic model, but even the hormonal model is dependent on mutagenic effects; it is just spontaneously occurring and not as a result of the oestrogen.

Chairman

1017. Dr. Boobis, would you like to ...? EC has the floor.

European Communities

1018. If you allow us to come in on this again, Alain Paris. [change of speaker.] Probably, the tumours that are detected, with regard to the administration of oestrogens, are revealed in a terminal stimulation process, and here we are combining initiation and promotion phenomena, knowing that promotion is extremely dependent on the oestrogen receptor. But this comes on top of the very premature initiation phenomenon which takes place via the activation, the bioactivation of the oestradiol molecule or its principal metabolites that will be found as residues, particularly oestradiol alpha.

Chairman

1019. Thank you. Dr. Boobis ... The United States have the floor.

United States

1020. I don't mean to interrupt Dr. Boobis, I was just going to note that I failed to discern a question in the statement that was just made and refer back to Canada's statement from earlier in the meeting regarding submission of evidence, and whether we are asking questions of the panel of experts that the Panel has comprised or whether the parties are providing evidence through their own experts at this point. Thank you.

Dr. Boobis

1021. I was going to make a somewhat similar comment. We are getting into the realms of interpretation of data. My view is that the data are interpretable as a non-mutagenic genotoxicity *in vivo*, if there is any response, with a threshold. Others have chosen to interpret the data differently. I was asked here for my opinion, my scientific opinion, based on the totality of the evidence. That is my opinion. So when we get into a discussion about the relevance of initiation and promotion in endocrine tumours, it critically depends upon the interpretation of the effects seen of these compounds. As I have just said, my view is that they do not support an *in vivo* initiation mechanism.

Chairman

1022. Thank you. Dr. Cogliano.

Dr. Cogliano

1023. Thank you. I think the comment that a lot of this is a question of interpretation, as Dr. Boobis has just said, is actually the heart of the scientific disagreement that we see here. I actually am not competent to tell whether there is or is not a threshold, but I can tell from my long experience in risk assessment that that is the fundamental scientific argument that is going on here. And so to be as helpful as I can to the Panel, the JECFA assessment felt that a threshold could be assumed even though there is some evidence of genotoxicity, because they felt that a hormonal mechanism was likely what was going on. Therefore they assumed there was a threshold and they computed the ADI and they went forward with an assessment. And it seems to me from reading the papers submitted by the European Commission as well as the arguments we have heard the last two days, they are unwilling to assume that there is a threshold. Sometimes I think the argument has been that because there may be some genotoxicity they are unwilling to assume a threshold, and sometimes I think they are unwilling to assume a threshold because there may be some other effects of these chemicals at low doses, but because they are unwilling to assume a threshold they say they cannot do a risk assessment because they cannot really predict a dose-response curve. Now I think those are the scientific arguments on both sides. I think that the way we phrase questions sometimes leads you to an answer of yes or an answer of no, but I think that is really the fundamental scientific issue that marks the difference between the JECFA assessment and the EC assessment; the willingness to conclude that there is a threshold for these compounds.

Ms Orozco

1024. Dr. Cogliano, I don't want to sound legalistic, but is that disagreement arbitrary? I am sorry, but we have to find ways to assess what has been done and sometimes there is a fair amount of information whereby professionals can disagree, scientists can disagree; other times the amount of information, the quality of the information, might not allow those variations. So what would be your assessment?

Dr. Cogliano

1025. I don't want you to put the word arbitrary in my mouth because I know that means something to lawyers and I don't fully understand what it means, but I would say it is a long-standing area of disagreement among scientists for many years about whether there are thresholds for carcinogens by different mechanisms. And the reason it is a controversy, I think, is the assumptions that scientists bring to risk assessment. There really are no data, we have heard that you cannot scientifically firmly establish that there is a threshold, but there are a lot of clues that a lot of scientists conclude that there is a threshold. But I think it really is an area of legitimate scientific disagreement that has gone on for many years. I don't wish to characterize that as arbitrary, I think it is more a matter of professional scientific judgement.

Ms Orozco

1026. … of course, legitimacy or reasonableness ...

Dr. Cogliano

1027. I don't think that there is a set of studies that can be done that will convince everybody one way or the other of a threshold or lack of a threshold.

Chairman

1028. I think this is also related to the so-called long-term latency period and cumulative effects arising from the cumulative exposure to the hormones at issue. I don't know whether or not the DNA repair mechanism is effective enough to deal with these kinds of long-term adverse effects. This is one thing I would like to hear from the experts. Dr. Boobis.

Dr. Boobis

1029. Well, of course experimentally when we are looking at the carcinogenic potential in animal models we dose the animals for what we call the lifetime, I mean it is not actually the full lifetime but it is a very substantial portion of a lifetime, two years in rats and 18 months in mice, and during that time any latency should be revealed. It takes into account accumulation of damage, DNA repair and any other components that might lead to a progression of effects, and indeed cancer is a multi-step process. It is well established now that you need several different overlapping stages before you get a malignant tumour and therefore these are encompassed within the scope of an experimental model. In the epidemiology studies one would have to look over a period of several decades to be able to account for such latency if the endpoint of concern was cancer.

Chairman

1030. What if DNA damage is done because of reasons we are not aware of due to the scientific uncertainty in the contemporary world and the adverse effects appear 30 or 40 years later; are current risk assessment techniques or mechanisms safe enough to deal with these kinds of problems? Dr. Boobis.

Dr. Boobis

1031. The paradigm we have, and there is some evidence to justify the case that this is a reasonable assumption, is that the effects observed scale to the lifetime of the organism, and so that is one of the reasons we use shorter-lived organisms in our toxicological testing. We use rats and mice which live for a couple of years; otherwise we would have to test for a lifetime in a longer-lived species which might be 40 or 50 years. So we are working on the principle that effects that are not evident within the lifetime of a rodent would not be evident, all other things being equal, within the lifetime of a human being. And there is actually very good evidence that that is the case. For a number of carcinogens that IARC have evaluated it takes approximately a quarter of a lifetime after an initial exposure for those tumours to become apparent, and that is true in rodents, it's true in dogs and it's true in humans. So I thing that the paradigm is reasonable that if there is going to be an effect manifest over a lifetime, it will be revealed in those experimental systems and therefore be predictive of lifetime effects in humans by and large.

Chairman

1032. Thank you. Dr. Boisseau and Dr. Guttenplan.

Dr. Boisseau

1033. Thank you, Mr. Chairman. I would like to go back to what Dr. Boobis has just said. If the protocol he has described permits us, where the experimental tests yield positive results, to predict an obvious effect on human beings after a reasonable period of time, why is it, if we are pleading for an absence of thresholds for this kind of oestrogen-related cancer, that the human epidemiological studies that have developed exponentially over the last twenty years have not been able to make any headway in highlighting this type of cancer?

Chairman

1034. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

1035. Actually, two points. You mention DNA repair in long-term tests. When DNA is damaged, DNA repair usually occurs relatively rapidly within hours and days. If the cell divides before repair occurs, you have a mutation. At least – I should not say that. If it divides and if the damage is of such a type that division does not produce an accurate reproduction of the original DNA molecule, then a mutation can result. Mutation is permanent, it cannot go away, and so once that has happened, there is some increased level of risk. But, as I mentioned before, most mutations are innocuous, most genes in which mutations occur are not going to result in, say, cancer or another adverse biological effect. So DNA repair takes care of most damage, but once the damage has occurred and has not been repaired before the cell divides it is permanent damage. As far as the threshold of oestrogens, and this I sort of throw out to the experts, if one assumes that there is a hormonal cause of cancer as a result of oestrogens as opposed to a genotoxic cause, the hormonal cause is assumed to result from pre-existing mutations, and then those pre-existing mutations, those cells containing the pre-existing mutations, are caused to turnover and divide because of the oestrogen stimulation. Unless there is a threshold for oestrogen stimulation, there should not be a threshold then for the hormonal effects of oestrogen, because the genotoxic effects, the effects of oestrogen, are indirectly genotoxic effects, they are promoting genotoxic effects. Now I don't know if there is a threshold for oestrogen receptors, I just throw that out as a piece of information.

Chairman

1036. Thank you. Dr. Boobis.

Dr. Boobis

1037. There is, and we have measured it. Endocrine-sensitive cells have a threshold for the mitogenic effects of oestradiol, it is absolutely clear, and we are not the only people, there have been many such studies to demonstrate that. I am talking about the mitogenic effects, I mean there are other effects that have been mentioned here and I am not qualified to discuss them in detail, but in terms of the mitogenic effect on, for example, the mammary gland, which is one of the targets we are considerably concerned about, there is a clear threshold for cell division. And that makes a lot of sense, you would not want circulating oestrogen to be stimulating cell division at whatever level it was, it has to be part of this homeostatic regulatory mechanism that allows the body to signal cell division when necessary by up-regulating the level of oestrogens.

Chairman

1038. Thank you. EC.

European Communities

1039. Chairman, we do appreciate the questions you have posed, they have been very appropriate in our view, and we have a number of scientists from our side – since we don't have other questions, we can make a statement in the form of a question, because they would like to intervene. These are important issues. There will be no new evidence, just comments on what has been said to clarify our debate.

Chairman

1040. Comments once again in the form of questions?

European Communities

1041. Yes. – Dr. Boobis, in the comments you have made, you refer to receptor-mediated events as thresholded and then be able to use them to create an acceptable daily intake. It is very clear that in the very low dose range oestrogen binds to oestrogen receptors, and then as the number of receptors are occupied, the receptors are inhibited as the dose of oestrogen goes up, until that response goes away, that is called the biphasic dose-response curve that has been known for 50 years. Then oestradiol begins to bind to androgen receptors, beginning to stimulate and inhibit an entirely different set of genes and an entirely different set of responses. If you begin your dose-response curve at a very high dose, what you will do is come to the bottom of a very bizarre set of events, that is the binding of oestrogen to androgen receptors. You will then use that as your NOAEL and calculate an ADI from it and completely miss the whole bottom part of the dose-response curve that is qualitatively different and completely unpredicted by what happens at the top part, and aside from the fact that you have an endogenous level of oestrogen that the oestrogen is operating against which argues against the threshold issue, could you explain how you can calculate an accurate ADI off of a hormone that operates through multiple mechanisms across a very wide dose-response curve that is never examined in a risk assessment study?

Chairman

1042. Dr. Boobis.

Dr. Boobis

1043. Mr. Chairman, do you wish me to answer this?

Chairman

1044. It's up to you.

Dr. Boobis

1045. I'll have a go. There are three components, one is the question of a threshold. I am sure Professor Vom Saal is familiar with the recent studies using transcriptomic experiments, looking at the totality of a gene expression profile in hormonally sensitive tissue, and there has been a clear threshold for every single gene transcript in those studies demonstrated. It is difficult therefore to understand how one can argue against a threshold. In our own studies using proteomic approaches, looking at the proteins that change within the cell, we have come to an identical conclusion. There are concentrations or doses of oestradiol-17β below which nothing changes – nothing. In answer to the second part of the question, how did we find a dose, a NOAEL where we could proceed to set an ADI. I said earlier it is based on a more holistic evaluation of the data. We are not concerned primarily with an intermediate response, we are concerned with adverse responses. What is the outcome for the organism, is there an adverse effect on reproduction, development, carcinogenicity? Based on such considerations on the totality of the available data we were content that we could identify a no-observable, and I stress this is by definition a no-observable adverse, and again I stress adverse, effect level. And this is the paradigm as adopted by all risk assessment bodies throughout the world. Thank you.

Chairman

1046. Thank you. Yes, EC.

European Communities

1047. Would I be able to ask a question back from that? The point here is that at the very very high end of the dose-response curve you are looking at adverse effects mediated through an entirely different system than the system that oestradiol operates through in a dose range a thousand times or so below the dose range that you are actually testing in your risk assessment, and I do agree that you are seeing adverse effects and that they will go away, the problem is that you then are not aware that there is a whole other set of adverse effects that can occur down below that, and I totally agree that there are different thresholds for turning on genes, and the endogenous level of oestradiol is high enough to exceed every single one of them. And that as you are adding extra oestradiol, you are altering the whole profile of genes that are expressed, and there was a PNAS paper by Toshi Shioda last year that showed that in exquisite detail.

Chairman

1048. Dr. Boobis.

Dr. Boobis

1049. The studies I mentioned were against the background of normal oestrogen levels. There were several papers published in the last three years showing that against that background there is no change from the control level in any transcript. As far as this ultra-low, U-shaped dose response curve is concerned, I would simply say that, as I mentioned earlier, this is one of those areas where there is considerable scientific controversy and I really don't think we can resolve it here; it is a major issue of controversial information. I could point to papers which show other results. Professor Vom Saal can point to many papers supporting his argument, quite correct. But as I say, currently, I think, it is fair to say within the scientific community it is an unresolved question.

Chairman

1050. Thank you. We have no confusion about that. Well, I don't know whether we have to continue this discussion on this particular point that this hour; we have 15 minutes to go before six o'clock. One question for EC.

European Communities

1051. Chairman, if you allow me, I will give the floor to one of our scientists who would like also to make one more point, this is Madam Annie Sasco, who is the expert on epidemiology.

European Communities

1052. OK. So I will be brief. I just want to make a point because it has been asked why did epidemiology fail to find any effect; and I am not sure epidemiology failed completely. Epidemiology, which is a study of the occurrence of disease and risk factors in populations, can be done at two levels. Levels of populations – and this was already discussed this morning when you looked at rates of disease potentially linked with hormonal factors in different countries. And this evidence is consistent with the hypothesis that these products may increase the risk of hormonal-dependent cancer, but there may be alternative explanations. And it's very complex, because cancer is a multi-factorial disease, so even beyond hormones there are also factors, other risk factors, which

intervene and play a role. It has long latency, we have to study for example diet 30 years ago to find the effect today, and therefore these population comparisons are just putting in some information that are not definitive. And the same can be said about time trends, and we have seen in most countries of the world we are still seeing increases in hormonal-dependent cancers, but the countries at the top of the scale are countries where these products have been used.

1053. The difficulty with these population statistics leads to the second type of epidemiological studies, where comparison is being done at the level of individuals; so we want to try to find out whether the people who have been exposed to these products are the ones getting cancer today. But when we look at an exposure like the one we are discussing, it is exceedingly difficult to do it, because all countries have been exposed, France as a whole country at the same time was exposed when this product was used, in the US almost everyone is exposed, so it's very difficult within a country to find differences and exposures between individuals, and I guess that is one of the reasons why it has not been attempted, because it will be a difficult exercise. But I think it could be attempted, at least in countries like the US, if we could identify population groups who only eat hormone-free meat and compare them with the ones eating hormone-treated meat. So I think we should not say that epidemiology will never be able to do it, it would be very difficult to do it, but maybe it could be attempted, and only now, because we needed to have 20 years, 30 years of exposure before we can see an impact. But I think for the whole topic, if we look at the effects on puberty, then in a way, from an epidemiology point of view it will be easier to see it, because we have to wait less years and maybe also because the difference is greater.

Chairman

1054. Thank you. Canada.

Canada

1055. Thank you, Mr. Chairman. I am very sorry to make this point so late in the day. Was that an argument, was that a statement, was that an expert testimony, was there a question in there somewhere for the experts? We are here at this point to hear from the experts, not from the EC delegation. We have heard enough, 19 volumes of evidence I understand, could you please clarify the role, even at this late hour, so that the time is not taken up by monologues.

Chairman

1056. I have no intention to further continue this discussion, so in the way of exchanging the views from the experts, the Panel has invited in experts in each delegation. So just leave this matter to the Panel with confidence and trust, and then I would like to give the floor to the US.

United States

1057. Thank you, Mr. Chairman. That was an interesting statement. I would note that the Panel expressly asked this question to the experts in question 26; it asked, which is relevant for this dispute, what the EC did in its purported risk assessment regarding epidemiological studies. And I think that Dr. Boisseau, Dr. Boobis, Dr. Coligano and Dr. Guttenplan all spoke to this issue. I won't put words in their mouths; if they would like to reiterate their answers to that question, they are welcome, but otherwise I would just note that this question has been asked and answered in the written responses.

Chairman

1058. So if delegations have no further questions or comments to be put to the experts, I have the intention of giving the floor to each and every expert to make concluding remarks if they so wish before we conclude our meeting this afternoon. The floor is yours, distinguished experts. Dr. Boobis.

Dr. Boobis

1059. Thank you Mr. Chairman. I have no specific comments. I hope that I have answered the questions put to me as clearly and succinctly as possible. I do believe that the information I provided in my written responses amplifies a number of those questions and hopefully will be a source of information as well to the Panel in their deliberations next week, and I thank you for your consideration and attention.

Chairman

1060. Thank you. Dr. Guttenplan first.

Dr. Guttenplan

1061. Although I have mentioned genotoxic effects of oestrogens, I would like to point out that in an adult woman, typical levels of oestrogen are 180 to 2,000 picomols per litre, and this is going to occur over their lifetime with the exception of menopausal state and pre-pubescence state. They are only about 2 in girls. So the potential genotoxic damage that is done in an adult would overwhelm that that could be done in a child. However, in boys the levels are even lower, and there I think we have to worry about developmental effects, and there has been less said on that – Dr. Sippell has been the major proponent of that – and I still think that these could be investigated epidemiologically or in some type of study. We might, as Dr. Boobis suggested, need a surrogate, perhaps saliva or urine, but I think it is perhaps the most important issue to address is the sensitivity of children. I should also mention hormone-sensitive cancers in post-menopausal women, it could be another concern. Post-menopausal women have levels of oestrogen that are similar to those of pre-pubescent girls, and if those levels are significantly elevated and you have a hormonal-sensitive cancer, you might be increasing the risk.

Chairman

1062. Thank you. Dr. Sippell.

Dr. Sippell

1063. I just would like to add that after these two days and hearing all the other experts' further comments to their written answers, I think that as much as children are concerned, we know really by no means enough and the data are really insufficient to tell or to be confident that this additional exposure from hormone-treated meat poses no risk. I am very much concerned.

Chairman

1064. Thank you. Dr. Boisseau.

Dr. Boisseau

1065. Thank you, Mr. Chairman. Over these past two days, I have done my best to provide as many clarifications as possible, responding to questions on the methodology used in the different expert

groups, in particular the JECFA which I know well. I insisted on the fact that the evaluation is a collective evaluation, conducted by competent and independent experts. This method, even if it has not been formalized or officially adopted, was known to everyone, and used practically throughout the world in the same way for all of the substances that were evaluated. I think that the hormones of which we have spoken were given special attention, and the data used were sufficient to enable us to come up with a risk assessment. Having said this, an assessment can always be updated to take account of scientific progress. Thank you Mr. Chairman.

Chairman

1066. Thank you. Dr. Coligano.

Dr. Coligano

1067. Thank you very much. I found these last two days extremely interesting and stimulating. I think that there are times I'm glad that I am in science and not in law, but I am sure that the rest of you are probably glad that you are in law and not in science. And I think what we are seeing here is the messiness of science as the data begin to accumulate but are not really sufficiently definitive to convince the entire scientific community, the way they are perhaps for something like tobacco smoking. And actually I think that the last comment that the leader of the US delegation made about question 26; our responses are emblematic of where these are. Question 26 was what are the differences between breast cancer and prostate cancer between the US and Europe; are they due to this factor? My own response was that it's one plausible cause but that there are many factors for breast cancer and the epidemiological studies cannot at this point sort out the difference between other dietary factors, physical activity, ethnic differences between the different countries, to be able to attribute causality to any particular cause with any reasonable confidence. So we are at this stage where we have suggestions but we cannot really resolve them, and I think that is what you see the scientists trying to struggle with. And when science is in this phase you will find scientists on both sides of issues, as we just heard about ten minutes ago. The idea of low dose effects of this is one of the major scientific controversies, and you do see scientists point to many studies on both sides of the issue, and it's not like going to be resolved any time soon. But I hope you have gotten a sense of the range of scientific thought, I think you actually can see that among the experts in the written answers and in these discussions. And I hope we have been helpful and I wish you luck in going on to making a decision on this important issue.

Chairman

1068. Thank you. Dr. De Brabander.

Dr. De Brabander

1069. A small final remark, Mr. Chairman. There is a lot said about risk assessment and I realize that indeed I was unable to help you very much on that item because I am an analytical chemist and control chemist, but as I expressed in my answers, I think there is more than human health only, and then the following of good veterinary practice only, there is also the influence of hormones on the behaviour of animals and animal welfare, there is also a concern about the environment. And I think in the future, concern with the environment will be more and more important, wherever it is in the world, and these are items I want to state in my final statement. Thank you.

Chairman

1070. Thank you all very much for your contribution and active engagement in the discussion on the issues at hand. I am particularly grateful for your patience, sitting with us for two full consecutive

days, even without having one minute coffee break. It was really difficult for us physically also. I myself, and I think the same is true of my colleagues in the Panel, we have learned a lot from our two-day meeting, even though I must confess that I did not fully digest your comments and replies on the technical issues; but I was very much impressed by the depth of the expertise and breadth of the knowledge you have brought to the area of your expertise, and I think it will greatly contribute to the Panel's work in the future. In the opening statement yesterday afternoon I stated that the Secretariat will provide a summary of the information and a transcript of the meeting for today and tomorrow. The Secretariat will do their best to make a transcript of the two-days meeting, but given the complexity of the issues and the difficulty to digest the terminology used during the meetings, they cannot be quite sure about whether they can make a complete transcript of the meeting. So at this point of time, the only thing I can say to you is that they will do their best to prepare that, but not with a 100 per cent guarantee. I don't know whether my colleagues in the Panel have additional comments before we conclude our meeting. Then I will conclude this two-day expert meeting now and the Panel will be meeting with the parties next week, starting on Monday, 2 October at 10 am. The meeting will be held in the same room as today. The meeting of the Panel with the experts is concluded. Thank you very much for all your contributions. Any point? Canada.

Canada

1071. Thank you, Mr. Chairman. Just a very simple question. Would the parties be provided with the transcript when it is provided?

Chairman

1072. I have been advised by the Secretariat that if the transcript is prepared, then it will be sent to the parties and experts for their comments.

Attachment 1

Slides shown by Dr. Sippell

WTO Panel on Hormones

Geneva, 27th & 28th September 2006

Paediatric Aspects

Wolfgang G. Sippell, MD, PhD

Professor of Paediatrics

Head, Division of Paediatric Endocrinology & Diabetology

Dept. of Paediatrics, Christian-Albrechts-Universität zu Kiel

University Children's Hospital

Kiel, Germany

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

- Although this dispute has already been going on for more than a decade, to my knowledge no paediatrician, let alone a paediatric endocrinologist, has been involved as a member on one of the expert committees.
- This is incomprehensible and paradoxical in view of the fact that prepubertal children are indisputably the most sensitive and vulnerable members of the population (smallest body size, longest life expectancy).
- I see my mission here as advocate of and spokesperson for children and their specific needs:

Children are not just small adults, but something very special!
They are our future!

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

Factors supporting the validity of the supersensitive RCBA for Estradiol (E_2) developed at the N.I.H., U.S.A. (Klein et al. 1994)

The novel finding of significantly higher (~8x) E_2 levels in prepubertal girls than in boys readily explains fundamental features of human biology for the first time:
(1)

- Earlier onset of puberty in girls than in boys (mean 1 year)
- Faster bone maturation in girls than in boys
- Lower adult height in women than in men (mean 13 cm)

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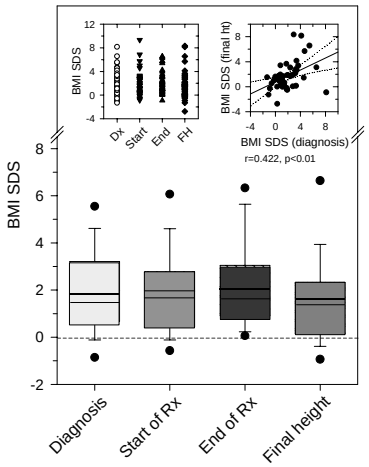
(2)

- Higher weight for height/BMI in girls than in boys at start of normal puberty

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

Chronic estrogen excess increases BMI in children

CPP Girls during/after GnRHa Treatment:
Weight Development (BMI – SDS) until Final Height



(N = 52)

Heger/Partsch/Sippell, JCEM 1999

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The novel finding of significantly higher (~8x) E_2 levels in prepubertal girls than in boys readily explains fundamental features of human biology for the first time:
(2)

- Higher weight for height/BMI in girls than in boys at start of normal puberty
- Incidence of Central Precocious Puberty (CPP) about 10x higher in girls than in boys
- Incidence of Constitutional Delay of Puberty much more common in boys than in girls

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

Ethical considerations

- For ethical reasons studies to investigate whether eating hormone-treated beef elevates estrogen levels in (prepubertal) children cannot be performed (physical/ psychological injury in healthy children).
- Epidemiological studies comparing adverse effects in matched populations of (healthy) children eating beef from hormone-treated and untreated animals would also be unethical.

→ **"Protect children from unnecessary clinical trials!"**

- Declaration of Helsinki
- Good Clinical Practice Guidelines
- EU Parliament Ruling ("Better Medicines for Children")

Attachment 2

Slides shown by Dr. Tritscher

International Food Safety Standards

- International food safety standards (Codex standards) are developed following the risk analysis paradigm
- They are based on independent international scientific risk assessments
- Codex Standards are an integral legal part in international food trade (WTO-SPS agreement)