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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:

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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.

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[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.

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[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.

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[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 any 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.

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[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.

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[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 "<u>if</u> exposure is at a <u>sufficiently high level</u>"[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]

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[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").