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UNITED STATES – 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/DS320/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 THE UNITED STATES 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. As noted in US Question 3 to the European Communities ("EC"), "systemic" and "direct" are terms used by the EC to describe its claims against the United States.[1] Each of the EC's "in conjunction with" claims, through which it seeks to recast several provisions of the *Understanding on Rules and Procedures Governing the Settlement of Disputes* ("DSU"), are couched as "systemic", while the EC claim of a US breach of DSU Article 22.8 (in and of itself) is described by the EC as a "direct claim." Neither of these terms appears in the DSU, nor are they part of customary rules of interpretation of public international law, as reflected in Articles 31 and 32 of the Vienna Convention on the Law of Treaties.

2. The question is not one of whether the EC has characterized one of its claims as "systemic" or "direct". Indeed, it is unclear what, exactly, the EC means when it uses these terms, other than to indicate in the case of a "systemic" claim that it is unable to identify a particular obligation in a specific provision of the DSU which the United States had allegedly breached. Rather, it is the role of the Panel to examine the actual obligations set out in the DSU as it is currently drafted, and to analyze the arguments of the United States and the EC in light of those obligations. Any EC claim must be grounded in the actual text of the DSU. As the United States has argued in several of its previous submissions, the EC claims which it terms "systemic" merely reflect how the EC would like to see the DSU redrafted, at least for purposes of this dispute. Through its "systemic" claims, the EC seeks license to depart from the agreed text of the DSU so as to insinuate new obligations into several provisions of the DSU. The United States has demonstrated that there is no basis for finding a US breach of these so-called "systemic" obligations.

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. Article 5.7 applies "[i]n cases where relevant scientific evidence is insufficient" to perform a risk assessment.[2] Accordingly, an analysis under Article 5.7 presupposes that there is, or may be, a breach of Article 5.1 or Article 2.2; otherwise, it would not be necessary for the Member maintaining a measure to assert that the requirements of Article 5.7 have been met.

4. In original proceedings brought against a measure, the question of whether the requirements of Article 5.7 have been met might arise in response to a claim that a measure is inconsistent with Article 2.2 or Article 5.1. In such a proceeding, the complaining party would have the burden of establishing a breach of Article 2.2 and/or Article 5.1. It would not be sufficient for the complaining party to demonstrate that the requirements of Article 5.7 have not been met in order "automatically" to

[1] US Questions to the EC, Question 3.
[2] Appellate Body Report, *Japan – Apples*, para. 179.

establish a breach of Articles 2.2 and 5.1. For example, where there is sufficient scientific evidence to perform a risk assessment, a Member may not provisionally adopt a measure pursuant to Article 5.7. However, this is a separate question from whether a risk assessment within the meaning of Article 5.1 has actually been performed.[3]

5. In this dispute, the Dispute Settlement Body ("DSB") has already ruled that the EC import bans on meat from cattle treated with the five hormones (for which the EC now asserts that the conditions of Article 5.7 have been met) breach Article 5.1. The EC does not claim to have performed a risk assessment consistent with Article 5.1. Against that background, the question in this dispute is whether the EC has established, in pursuing its claim under Article 22.8, that the EC has provided a solution to the nullification or impairment caused by the breach of Article 5.1 because the conditions of Article 5.7 have been met. Since the Article 5.7 conditions have not been met, the EC has not demonstrated that it has provided a solution to the nullification and impairment found by the DSB. In that sense, the failure to meet the requirements of Article 5.7 "automatically" leads to the conclusion that the Article 5.1 breach found by the DSB has not been removed.

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. As noted in the US response to Panel Question 49 after the first substantive meeting, the EC contacted the United States in 1999 to inform relevant US regulatory agencies of its completion of the 1999 Opinion on the six hormones at issue in the *EC – Hormones* dispute. At that time, the US Food and Drug Administration ("FDA") and Department of Agriculture ("USDA") reviewed the documents put forward by the EC. The response to those documents is contained in Exhibit US-21. The United States and the EC then met during the summer of 1999 to discuss the results of the EC's 1999 Opinion.

7. We have been unable to locate any records indicating that the EC provided its 2000 Review or 2002 Opinion to US authorities for a similar review or that it requested a scientific conference or discussions on the conclusions of those documents similar to those held in 1999. Similarly, we have no record of a requested discussion or conference on the scientific underpinnings of the EC's ban once it asserted in the fall of 2003 that it had developed a risk assessment and brought its measure into conformity with DSB recommendations and rulings.

8. The United States and the EC held a video conference in the fall of 2003, during which the EC provided a brief PowerPoint presentation summarizing its amended ban. However, the EC did not provide any information on its 2000 Review or 2002 Opinion, nor did it present any information on the scientific conclusions and analyses it viewed as supporting its amended ban. A copy of this presentation may be found in Exhibit US-22.

[3] At the same time, the United States recognizes that a responding Member would likely only have raised Article 5.7 in the context where the responding Member does not claim to have performed a risk assessment meeting the requirements of Article 5.1 or that there is sufficient scientific evidence for purposes of Article 2.2. In that situation, there would appear to be no dispute that there would be a breach of Article 5.1 or 2.2 if the requirements of Article 5.7 are not met, and in that sense the breach of Article 5.1 or 2.2 would be "automatic."

9. The United States sent the EC an SPS Article 5.8 request in the fall of 2004, to which the EC responded on May 19, 2005. A copy of the Article 5.8 request and the EC's response may be found at Exhibit US-23. The EC's response contained internet links for the 2000 Review and 2002 Opinion.

10. At no point in time prior to the initiation of this dispute was the United States in possession of all of the "17 Studies" ostensibly underpinning the EC's "risk assessment." These materials were not provided by the EC in its response to the US Article 5.8 request and were produced in a piecemeal fashion throughout these proceedings. We have discussed the EC's failure to produce these studies in detail in the US Rebuttal Submission (paras. 19-22) and have chronicled the (lack of) availability of these studies in Table 1 to that Submission.

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 17ß 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.

11. The EC has not assessed the existence and level of risks from failure to observe good veterinary practices with respect to the administration of estradiol 17ß as a growth promoting hormone to cattle in the United States. In fact, the EC has not even seriously argued in the course of these proceedings that it has done so.

12. As noted by the United States in several of its submissions, the EC presented a number of unrealistic misuse scenarios. However, the actual occurrence of these scenarios in US feedlots is purely speculative and unsupported by evidence.[4] For example, in its 1999 Opinion, from pages 30-31 (§ 3.3), the EC presents several hypothetical misuse scenarios but fails to assess the probability that any of these scenarios would occur. The EC postulates that ears from cattle containing growth promoting implants will enter the human food supply. When the United States asked whether the EC had provided any evidence that this has ever occurred or would ever occur, the experts (Drs. Boobis and De Brabander) noted that there was no such evidence. The EC also concludes that there is a risk that a black market will exist in the United States for estradiol 17β. (1999 Opinion, § 3.3.3). However, the only evidence on the record regarding the existence of a black market demonstrates that such a market exists in the EC, where use of the hormone as a growth promoter has been banned. Not only does the EC fail to provide evidence of or assess the potential for misuse in its 1999 Opinion, even if one were to assume misuse, the EC has failed to provide any evidence that violative residue levels would result except in the most extreme overdosing circumstances.[5]

13. In its Exhibit EC-73, the EC discusses several hypothetical misuse scenarios but similarly fails to assess, in any meaningful way, the likelihood of the occurrence of any of these scenarios in US feedlots. For example, the EC asserts that "stacking" of implants (*i.e.*, treatment with more than one dose of an implant at the same time) is commonplace in the United States.[6] However, the evidence cited by the EC to support this argument – a guidance document from the University of Nebraska – does not stand for this conclusion. This fact was confirmed by the author of the guidance cited by the EC.[7] Further, the EC fails to examine the actual workings of the US food safety system both in this document and in each of the three Opinions comprising its "risk assessment." The United

[4] The United States discusses the EC's failure to assess the risk of misuse (or failure to satisfy good veterinary practices) at length in its Rebuttal Submission (pages 21-30) and its Oral Statement at the Second Substantive Meeting (Expert Issues) (paras. 60-67).

[5] *See* US Rebuttal Submission (pages 21-30); Dr. Boobis' Response to Panel Question 62.

[6] Exhibit EC-73.

[7] *See* Letter from Dr. Dee Griffin, Exhibit US-28; US Rebuttal Submission, paras. 60-63.

States has discussed the actual workings of the US food safety system at length and has demonstrated that the EC's speculation that a risk of failure exists is not based on any evaluation of any evidence.[8]

14. It is essential to recall the views of the scientific experts on the issue of whether or not the EC has indeed assessed the risk of a failure to meet GVPs. Dr. Boisseau noted that "as the [EC] did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the scientific evidence referred to by the [EC] assesses the risk to human health from residues resulting from these misuses/abuses."[9] Dr. Boobis agreed, stating: "[t]here was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies. Indeed, the SCVPH (2002) simply noted that '[t]herefore, these data have to be considered in any quantitative exposure assessment exercise', without undertaking such an exercise."[10] While Dr. De Brabander appears to disagree with Drs. Boobis and Boisseau, his responses fail to indicate whether or not he is of the opinion that the EC actually assessed the risk of misuse, and in several instances his opinions are simply based on anecdotal information and policy considerations, rather than scientific evidence or citations to the EC's purported risk assessments.[11]

15. Finally, it is necessary to recall that, even if one assumed that the EC actually assessed the risk of a failure to meet GVPs, the scientific evidence put forward by the EC indicates that violative residues in meat would only occur as a result of that failure in the most extreme circumstances. Dr. Boobis provides a thorough review of the EC's materials in his response to Panel Question 62 (at pages 50-52). The United States has also reviewed these EC materials and commented on their failure to demonstrate violative residues except for in the most unrealistic scenarios.[12]

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 17ß 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 17ß for growth promotion purposes?

16. To date, the EC has presented only one study (out of 127 Exhibits) which addresses genotoxicity of estradiol 17ß *in vivo*.[13] In Exhibit EC-125, rats were treated with 5 milligrams of estradiol 17ß. This dose of estradiol 17ß resulted in a two-fold increase in the number of mutations in mammary tissue. However, as discussed in the meeting with the experts, the results of this study are highly questionable for a number of reasons, and the doses involved in the study are not comparable

[8] *See* US Rebuttal Submission, para. 55; US Comments on the Experts' Responses, paras. 105-106.

[9] Dr. Boisseau Responses (Question 48), p. 24.

[10] Dr. Boobis Responses (Question 48), p. 42. *See* Dr. Boobis Responses (Question 62), p. 52 ("the data generated by the EU research in question do not provide any indication that it is not possible to conduct a risk assessment of the hormones used as growth promoters.")

[11] *See*, *e.g.*, US Comments on the Responses of the Experts, para. 107.

[12] *See* US Comments on the Experts' Responses, Section C.6; US Rebuttal Submission, Section II.B.4.

[13] In paragraph 43 of its Comments on the US and Canada's Comments on the Experts' Replies, the EC claims to have "sufficient and constantly growing evidence from studies in vivo that show the direct genotoxicity of oestradiol 17ß and its catechol metabolites ...". However, US review of the studies listed in paragraph 43 reveals that only one, EC-125, demonstrated genotoxicity of estradiol 17ß *in vivo* (and only then at irrelevant doses) while the other studies were performed only with catechol metabolites. This fact was confirmed by Dr. Metzler, member of the EC delegation, at the meeting with the experts on 28 September 2006. The distinction between estradiol 17ß and its catechol metabolites is important because the EC has presented no evidence to show that the catechol metabolites are present *in vivo* at levels comparable to those which produce genotoxic effects *in vitro*. Moreover, the EC has presented no evidence to show that consumption of estradiol 17ß residues in beef affects the production of catechol metabolites whatsoever.

to residue levels found in meat from cattle treated with estradiol for growth promotion purposes.[14] Indeed, the doses are exponentially greater than those necessary to elicit biological or endocrine effects (in other words, they are well above the hormonal threshold).

17. To compare the dose of estradiol 17ß used in EC-125 to levels found in meat from cattle treated with growth promoting hormones, it is necessary to examine the dose relative to body weight. A laboratory rat weighs approximately 250 grams. Therefore, the dosage administered to the rats in EC-125 was 5 milligrams/250 grams, or 20 milligrams/kilogram. If a human (average weight of 70 kg.) were treated with an equivalent dose of estradiol 17ß, the dose would be 1400 mg (20 milligrams/kilogram x 70 kg). This dose is exponentially greater than residue levels found in meat from cattle treated with estradiol for growth promotion purposes. According to JECFA,[15] a conservative estimate of the amount of estradiol 17ß in a 250 gram serving of meat from treated cattle is between 15 and 25 nanograms, or 0.000015-0.000025 milligrams. In other words, in relative terms, the dose administered to the rats in the EC's study (Exhibit EC-125) is more than 50 million times greater than the amount of estradiol residues consumed by humans in meat from treated cattle.

18. Therefore, the dose of estradiol 17ß administered to rats in EC-125 was astronomically higher than that derived from eating a serving of beef from treated cattle. The difference is even greater when one takes into account the different routes of administration of estradiol 17ß. The rats in the study were treated estradiol 17ß via subcutaneous implants, which results in very high bioavailability. In contrast, only a small percentage (≤ 10%) of orally-ingested estradiol 17ß is bioavailable due to rapid metabolism in the liver and small intestine. So, not only was the dose exponentially greater in the rat study but the dose was much more bioavailable than would be the case from consuming residues in meat. For these reasons, this study is not relevant to the purported risk to human health associated with eating meat from cattle treated with growth-promoting hormones.

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?

19. Under the US legal system, the applicable authorities and procedures are set out in Sections 301-309 of the Trade Act of 1974, as amended (codified at 19 U.S.C. 2411-2419) (commonly referred to as "Section 301").

20. Suspension of obligations: On July 12, 1999, the arbitrator determined that the level of nullification and impairment suffered by the United States in this dispute was $116.8 million per year, and that the United States was entitled to suspend the application of tariff concessions up to that amount. On July 26, the DSB authorized the United States to suspend the application of tariff concessions in this amount. In accordance with the arbitrator's report and DSB authorization, the USTR determined that appropriate action under Section 301 in response to the EC's failure to comply with the DSB recommendations and rulings was to suspend the application of tariff concessions and increase tariffs on a specific list of EC products with an annual trade value of $116.8 million. The USTR then published a *Federal Register* notice announcing the suspension of concessions in the form of increased duties on specific products of the EC.

21. Termination of Suspension: Section 301 provides that the USTR may terminate an action previously taken under Section 301 if, *inter alia*, the DSB adopts a report finding that the rights of the

[14] *See* paragraphs 27-29 of US Oral Statement at the Second Substantive Meeting (Expert Issues).

[15] *See* "Evaluation of certain veterinary drug residues in food", Fifty-Second Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series: 893 (2000) ("52nd JECFA Report"), p. 83. (Exhibit US-5).

United States under the trade agreement are not being denied. Section 301 requires USTR to consult prior to terminating any action. Upon making such a determination, USTR would publish a notice in the *Federal Register* announcing the termination of the suspension of concessions and the restoration of regular MFN rates of duties on the affected products.

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?

22. Since the United States is not the complaining party, there is no challenge to an EC measure in this dispute as such. Rather, the question is whether the EC has demonstrated, within the meaning of Article 22.8 of the DSU, that the EC has removed its WTO-inconsistent measures or has provided a solution to the nullification or impairment.[16] If the EC has simply continued its WTO-inconsistent measure, then there would be no solution to the nullification or impairment. If the EC has not demonstrated that it has solved the nullification or impairment through a new or revised measure, then the EC has not met its burden under Article 22.8. Accordingly, the United States has not argued that the EC's amended bans are or are not new measures for purposes of the DSU. Rather, we view the pertinent question to be whether or not the EC's bans in fact bring it into conformity with the DSB recommendations and rulings in the *Hormones* dispute. If there were a DSB finding that the EC has complied by basing its permanent ban on estradiol on a risk assessment within the meaning of SPS Article 5.1 and satisfying the four cumulative conditions of SPS Article 5.7 for its provisional bans on the other five hormones, then there would no longer be a basis to apply the suspension of concessions or other obligations. This would be the case whether the EC's ban was a new measure or a continuation (albeit with modification) of the previous measure.

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?

23. As the responding party, the United States has not made any claims of an EC breach of its WTO obligations. The EC, as the complaining party, is responsible for bringing such claims and satisfying its burden of proof for each claim. One of the EC claims in this dispute is that the United States has breached its obligations under DSU Article 22.8, which sets out the conditions under which a Member suspending concessions or other obligations must cease to apply the suspension against another Member. In order to satisfy its claim under DSU Article 22.8, the EC must demonstrate that it has either removed the WTO inconsistent measure(s) or that it has provided a solution to the nullification and impairment of benefits.

24. The EC clearly has not removed its import bans nor has it claimed to have done so. Therefore, in order to satisfy its burden in this proceeding, the EC must demonstrate that it has brought its measure into conformity with the DSB recommendations and rulings in the *Hormones* dispute. Those recommendations and rulings include findings of EC breaches of SPS Articles 5.1 and 3.3. The EC argues it has satisfied the DSB recommendations and rulings by basing its permanent ban for estradiol on a risk assessment and satisfying the four conditions of SPS Article 5.7 for the other five hormones in lieu of a risk assessment. These arguments call for findings as to whether or not the EC has in fact demonstrated that it has brought itself into conformity with the DSB's recommendations and rulings, as these findings are integral to the EC's Article 22.8 claim.

[16] No party has argued that the third prong of the Article 22.8 test is involved here – reaching a mutually satisfactory solution.

25. The reference to SPS Article 2.2 in paragraph 27 of the US Rebuttal Submission was made in the context of describing how SPS Article 5.7 functions as a qualified, temporary exemption under the SPS Agreement. The reference was not intended to elicit a finding of a breach of SPS Article 2.2. Rather, the appropriate finding would be that the EC, in failing to satisfy the conditions of Article 5.7, has not solved the nullification and impairment of benefits arising from its failure to base its measures relating to the five other hormones on a risk assessment within the meaning of SPS Article 5.1. The EC concedes that it has not based these measures on such an assessment; therefore, the EC has not brought its measures into conformity with the DSB recommendations and rulings.

26. The United States believes that a finding of compliance or non-compliance with the requirements of SPS Article 5.2 would be appropriate as part of the Panel's analysis of whether the EC has based its measure on a risk assessment within the meaning of SPS Article 5.1. Article 5.2 requires that risk assessments take into account certain elements, including available scientific evidence; relevant processes and production methods; and relevant inspection, sampling and testing methods. Article 5.2 is not mutually exclusive of SPS Article 5.1; rather, it sets out the specific components of the risk assessment on which Members are required to base their measures for purposes of SPS Article 5.1. If the EC has not satisfied the requirements of Article 5.2, it has not conducted a risk assessment, as appropriate to the circumstances. Its measure (permanent ban on estradiol) therefore cannot be based on a risk assessment within the meaning of SPS Article 5.1.

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 17 ß or whether they apply also in relation to the provisional ban imposed on the other five hormones?

27. US arguments regarding a violation of SPS Article 3.3 apply in relation to each of the EC bans on meat from cattle treated with growth promoting hormones for which international standards exist. In other words, US arguments relate to each of the hormones at issue except for melengestrol acetate ("MGA"), for which JECFA has conducted a risk assessment, set an ADI and proposed an MRL, but for which Codex has not adopted an MRL. SPS Article 3.3 requires that Members base their measures on international standards where they exist and only permits Members to diverge from such standards if there is a scientific justification for doing so. For purposes of this dispute, that scientific justification could have taken the form of a properly conducted risk assessment for estradiol or satisfying the four conditions of Article 5.7 for testosterone, progesterone, zeranol and trenbolone acetate. The United States has demonstrated that the EC has failed to provide such a justification.

28. The United States has demonstrated that the EC has failed to satisfy the conditions of Article 5.7 for its provisional ban on MGA because, among other things, there is sufficient scientific evidence to conduct a risk assessment for MGA and the EC has not based its provisional ban on MGA on available pertinent information. The United States has also demonstrated that the EC failed to satisfy the conditions of Article 5.7 for the other four provisionally banned hormones (testosterone, progesterone, zeranol, and trenbolone acetate).

ANNEX C–4

REPLIES OF THE UNITED STATES TO QUESTIONS POSED BY THE EUROPEAN COMMUNITIES AFTER THE SECOND SUBSTANTIVE MEETING

(18 October 2006)

EC Questions to the 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. Of course, it is not US measures that are at issue here. The European Communities ("EC") has chosen to ban the import of US meat and meat products from cattle treated with each of the six hormones for growth promotion purposes and it is therefore an analysis of the EC's "risk assessment" and basis for its five "provisional bans" that is essential to this dispute. That being said, we are happy to provide more information for background, although we note that this is the sort of question that the EC could have posed earlier to better inform its own risk assessment.

2. The US Food and Drug Administration ("FDA") conducted quantitative exposure assessments for each of the hormones approved to promote growth in cattle. The procedures that FDA uses to evaluate the safety of edible products from animals treated with veterinary drugs are publicly available and described in detail on the FDA web site.[1] The exposure assessment component of the evaluation of the six growth-promoting hormones can be summarized as follows.

3. For each of the six hormones, FDA required the sponsors to conduct extensive residue studies. These studies provided information on total residue depletion and the metabolic fate of each hormone in edible tissues from cattle (muscle, liver, kidney and fat).

4. For each of the three synthetic hormones, sponsors also performed extensive toxicological testing in experimental animals[2] to determine the dose at which the hormone produced an adverse effect and the dose at which no effect was observed (no effect level or "NOEL"). The NOEL of the most sensitive toxicological effect (*e.g.*, reproductive, developmental, tumorigenic) in the most sensitive species examined (*e.g.*, rat, mouse, rabbit) was then divided by an appropriate safety factor to determine an acceptable daily intake ("ADI"). The ADI was then used to calculate a safe concentration for each edible tissue from cattle as follows: safe concentration = ADI × 60 kilograms (weight of average person) ÷ grams consumed per day. The food consumption factors currently used by FDA are: muscle, 300 grams; liver, 100 grams; fat and kidney, 50 grams each.[3] FDA determined that for each of the synthetic hormones, the total residues (*i.e.*, residues of toxicological concern) were less than those calculated from the respective ADI. Therefore, FDA concluded that consumption of these residues in edible tissues from treated cattle does not pose a risk to human health.

[1] http://www.fda.gov/cvm/Guidance/published.htm, Guidance 3

[2] This testing is also explained in FDA Guidance 3.

[3] At the time the hormones were approved, an even more conservative food basket was used and it was assumed that on any given day a person might consume up to 500 grams of muscle, 250 grams of liver, 167 grams of kidney, or 125 grams of fat.

5. For the three natural hormones, FDA did not establish ADIs and concluded that human safety can be assured without the need for extensive toxicological testing in experimental animals. This is because 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. FDA concluded that no additional physiological effect will occur from chronic ingestion of animal tissues that contain a residue level of natural hormones equal to 1% or less of the amount produced daily by the segment of the population with the lowest endogenous production.[4] Using food consumption factors, FDA set permitted increased daily exposures of 0.06 micrograms for estradiol, 1.50 micrograms for progesterone, and 0.32 micrograms for testosterone. To obtain FDA approval for the natural hormones, the drug's sponsor was required to demonstrate that residues of each hormone in edible tissues from treated cattle did not exceed the safe concentration. This requirement was satisfied for all three of the natural hormones.

6. The exposure assessment conducted by JECFA for each of the six hormones was described in detail by the JECFA representative at the meeting with experts on 27-28 September 2006. References describing JECFA's risk assessments for the hormones can be found in the answer to Question 2 below.

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).

7. Again, this dispute settlement proceeding is not concerned with the measures of the United States or any risk assessments of the United States. And under Article 3.3 of the SPS Agreement the EC has an obligation to be familiar with the relevant international standards, guidelines or recommendations. The United States wonders if the EC's question is an admission that the EC has failed to familiarize itself with the relevant JECFA material.

8. That being said, we are happy to provide more information for background, although we note that this is the sort of question that the EC could have posed earlier to better inform its own risk assessment. As explained in the FDA Guidance[5] referenced in the response to Question 1, FDA requires that total residue depletion studies be conducted using the dose that is the highest intended treatment level and that these studies should model the exposure received by the target animal. In the case of the six hormones in question, the highest intended treatment level was (and still is) one implant per animal, consistent with good veterinary practice.

9. JECFA completed quantitative exposure assessments for each of the six hormones. The process for conducting these assessments was described by the JECFA representative at the meeting with the experts. Food and Nutrition Paper ("FNP") 41/12 provides extensive compilations of residue data for each of the natural hormones and the analysis includes estimates of exposure from the consumption of the four edible tissues (muscle, liver, kidney and fat) from treated animals.

[4] Sensitive subpopulations are prepubertal girls for testosterone and prepubertal boys for estradiol 17 and progesterone.

[5] http://www.fda.gov/cvm/Guidance/published.htm

10. The exposure assessment for the three natural hormones, as well as the available residue data, metabolism data and analytical methods can be found at the JECFA website.[6] The WHO Technical Report Series publication 893 summarizes all of the relevant findings on additional estimated exposure from consumption of tissues from hormone-treated animals. For total estrogens, the highest excess intake (from eating beef from treated cattle) was 30-50 nanograms per person per day. For progesterone, the estimated maximum daily exposure was approximately 500 nanograms per day, and for testosterone, about 60 nanograms per day. These figures represent less than 2% of the JECFA ADI for estradiol, 0.03% for progesterone and about 0.05% for testosterone. That is, tissues from hormone-treated animals present hormone residues that are a minuscule percentage of daily allowances for ingestion of such hormones.

11. The JECFA residue, metabolism and analytical method reports for the three synthetic hormones may be found at the website listed above. Individual reports are contained in FAO FNP 41, 41/2, 41/13, 41/16 and 41/17. For each hormone, the approach used by JECFA was to establish an ADI and recommend MRLs that are consistent with the maximum theoretical residues determined by the ADI established on a µg/kg body weight basis.

12. JECFA's evaluations of the six hormones are based on data provided by sponsors which, in general, reflect good veterinary practices. The United States notes that, in continuing to raise the issue of good veterinary practices, the EC only underscores its failure to meet its WTO obligations in this regard. The experts have confirmed that the EC itself has failed to properly examine the likelihood of misuse or abuse of the hormones at issue as it was obligated to do pursuant to Articles 5.1 and 5.2 of the SPS Agreement.[7]

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?

13. Drs. Cogliano, Sippell and Guttenplan postulated that it is not possible to define with precision the low-dose response curve for estradiol. However, it is necessary to examine this discussion in light of the available scientific evidence relating to estradiol and the experts' opinions on that evidence. The scientific evidence indicates that there is a threshold for the genotoxic and carcinogenic effects of estradiol. Genotoxic and carcinogenic effects are only observable at very high doses (both *in vivo* and *in vitro*) at or above this threshold. This threshold is orders of magnitude greater than the levels of estradiol found in residues in meat from cattle treated for growth promotion purposes. There is no scientific evidence demonstrating adverse effects at doses lower than the hormonal threshold.

14. Dr. Guttenplan concluded that there is no risk for carcinogenicity below the acceptable daily intake level ("ADI") for estradiol at the meeting with the experts, thereby indicating that any

[6] www.fao.org/ag/agn/jecfa/archive_en.stm

[7] *See* Dr. Boobis Responses (Question 62), p. 58 ("[t]he evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion"); Dr. Boobis Responses (Question 48), p. 42 (the EC has made "no attempt to evaluate the risks" from misuse, either in its Opinions or in underlying studies); Dr. Boisseau Responses (Question 51), p. 25 ("the [EC] did not conduct a quantitative risk assessment from growth promoters, [and that] it is not possible to say the scientific evidence referred to by the [EC] assesses the risk to human health from residues resulting from these misuses/abuses.") *See* Appellate Body Report, paras. 205-207.

carcinogenic effects would be a result of doses above the threshold (levels exponentially greater than those found in residues in meat from treated cattle). Dr. Boisseau noted that "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity."[8] As noted by Dr. Cogliano, "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans."[9] Finally, Dr. Boobis stated that "[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity."[10] In other words, carcinogenic effects were only observable at levels at or above the hormonal threshold. In the absence of any scientific evidence of adverse effects at doses below the threshold, arguing about the shape of the dose-response curve below the threshold is not informative. In other words, there is no evidence that estradiol will cause adverse effects below a definable threshold. The EC has failed to present any such evidence in the course of these proceedings.

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.

15. As indicated in our previous response, the question of the shape of the dose response curve at low doses is not reflective of any scientific uncertainty relevant to the risk at issue given the lack of scientific evidence of a risk below the threshold for estradiol. The United States summarized the state of scientific evidence relating to the genotoxicity and carcinogenicity of estradiol in its response to Question 3 above. The EC has attempted to cast this lack of evidence of a risk at low doses as a relevant "scientific uncertainty." But this lack of evidence of a risk cannot be construed in turn as evidence of a risk or as a basis for the EC's ban.

16. By arguing the presence of "scientific uncertainty" in a situation in which there is no evidence of a risk at relevant exposure levels, the EC appears to be seeking nothing less than an assurance that there will never be evidence of a new risk from estradiol at some point in the future. As argued by the United States and discussed by the Appellate Body, this is an uncertainty "that theoretically always remains since science can never provide absolute certainty that a given substance will not ever have adverse health effects. We agree with the Panel that this theoretical uncertainty is not the kind of risk which, under Article 5.1, is to be assessed."[11] This type of uncertainty is not evidence of a risk, nor may it serve as the basis for the EC's ban on meat and meat products treated with estradiol for growth promotion purposes.

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?

17. Please see the US response to Panel Question 20.

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?

[8] Dr. Boisseau Responses (Question 16), p. 12.
[9] Dr. Cogliano Responses (Question 18), p. 1.
[10] Dr. Boobis Responses (Question 16), p. 19.
[11] Appellate Body Report, para. 167.

18. The 11th Report on Carcinogens notes 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." Paragraph 51 of the US First Written Submission states that "[w]hile tissue concentrations of estradiol 17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels."

19. The United States fails to see a discrepancy between these statements but is pleased to be able to clarify the issue for the EC through reference to the EC's own exhibits. It appears that the source of the EC's confusion is use of the word "normal" in the Report on Carcinogens. In this (biological) context, "normal" is a relative term which depends on the endogenous, baseline levels of estradiol 17β present in the animal treated with growth-promoting hormones. For example, the "normal" levels of estradiol 17β in steers (male cattle lacking testes) will be extremely low. It stands to reason, therefore, that treatment of steers with estradiol 17β to promote growth may increase concentrations of estradiol 17β in edible tissues to levels that are above "normal" for this type of animal. However, as illustrated in Table III of EC-34[12], this increase may be small (1.1 to 2.3-fold) and, as illustrated in Figure 1 of EC-51A, is not detectable in every animal. Female cattle have higher "normal" levels of estradiol 17β than steers and these levels may be more variable due to changes in production of estradiol 17β by the ovary throughout the (21-day) reproductive cycle. Treatment of female cattle (heifers) with estradiol 17β to promote growth may also result in increased estradiol 17β concentrations in edible tissues of heifers, and according to Table III of EC-34, this increase is similar to that observed in steers (1.9-fold).

20. The basis for the US statement that "this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels" is clearly illustrated by comparing the levels of estradiol 17β in edible tissues of treated steers and heifers shown in Table III of EC-34 with the naturally-occurring levels of estradiol 17β in cattle shown in Table II of EC-34. Concentrations of estradiol 17β in muscle of treated steers and heifers ranged from 3-17 pg/g, while naturally-occurring concentrations range from 1.3-14 pg/g in steers, 12-13 pg/g in heifers, and 16-860 pg/g in pregnant cattle. Therefore, even though veterinary use of estrogens to promote growth can increase estrogens in cattle to above "normal" levels (11th Report on Carcinogens), this increase is well within the range of naturally observed levels (US First Written Submission).

Q2. What was the reason to conclude for the first time in the 2002 US Report on Carcinogenesis that estrogens (including oestradiol-17ß) 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?

21. As explained in the second paragraph of the Introduction to the 11th Report on Carcinogens (EC-101 and US-26), the Report on Carcinogens lists all substances which are known (or reasonably anticipated to be) human carcinogens and to which a significant number of US residents are exposed. This report is routinely prepared every two to four years by the National Toxicology Program and published by the Department of Health and Human Services.[13] It follows, then, that each Report on Carcinogens will include updated information on each carcinogen as that information becomes available.

[12] In Exhibit EC-34, Daxenberger *et al*. present findings derived from a comprehensive search of the scientific literature on estradiol 17β residues in edible tissues of cattle.

[13] http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540

22. The 10th and 11th Reports on Carcinogens were published in 2002 and 2005, respectively. Steroidal estrogens were first listed as "known to be a human carcinogen" in the 10th Report.[14] Both the 10th and 11th Reports include a section that discusses the evidence for genotoxic effects of steroidal estrogens. This section is virtually identical between the Reports. Cited in this section are two references: one article published in 1996[15] and the 1999 IARC Monograph on Hormonal Contraception and Post-menopausal Therapy. It is therefore clear that the statements on genotoxicity in both the 10th and 11th Reports on Carcinogens – published in 2002 and 2005, respectively – were based primarily on the findings of the 1999 IARC Monograph and not prompted by new developments in scientific research that became available after 1999.

23. Again, it should be emphasized that the findings of the Report on Carcinogens and the IARC Monograph speak to the general risk from estrogens at levels exponentially higher than those found in residues in meat from treated cattle. The Appellate Body and the original *Hormones* panel reviewed the earlier version of the 1999 IARC Monograph often cited by the EC in these proceedings and confirmed that studies such as the Monograph:

> constitute[d] general studies which d[id] indeed show the existence of a general risk of cancer; but they d[id] not focus on and d[id] not address the particular kind of risk here at stake – the carcinogenic or genotoxic potential of the residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes.[16]

24. The potential for adverse effects from hormones at these high levels is not in dispute.[17] The materials and findings cited by the EC (1999 IARC Monograph; 11th Report on Carcinogens) are not, however, evidence of a risk from meat from cattle treated with estradiol for growth promotion purposes.

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?

25. The procedures used by FDA for assessing the human safety of veterinary drugs used in food-producing animals are publicly available and described in detail at http://www.fda.gov/cvm/Guidance/guideline3pt2.html. For these compounds, FDA focuses its evaluations on the risks of intermittent, chronic exposure of humans to relatively low concentrations of residues. FDA tailors the type of toxicological testing required to show the safety of each compound according to its proposed use, probable exposure of humans to both the parent compound and its metabolites, and its possible effects as observed in biological systems. For some compounds,

[14] Prior to the 10th Report on Carcinogens, conjugated estrogens were listed in the 4th Report in 1985 as "known to be human carcinogens″ and a number of individual steroidal estrogens (non-conjugated, including estradiol-17β, estrone, ethinylestradiol, and mestranol) were listed as "reasonably anticipated to be human carcinogens."

[15] Yager JD and Liehr JG. Molecular mechanisms of estrogen carcinogenesis. Annu Rev Pharmacol Toxicol 1996; 36: 203-232.

[16] Appellate Body Report, *EC – Hormones*, para. 200.

[17] *See*, *e.g.*, US First Written Submission, para. 141; US Rebuttal Submission, paras. 38-39.

only a minimum of testing is required while other compounds may require more extensive toxicological evaluation.

26. In line with the 11th US Report on Carcinogens, FDA considers estradiol 17β to be a human carcinogen. (However, it should be emphasized that the carcinogenicity of estradiol 17β in humans is based largely on epidemiological studies of women taking estradiol 17β as post-menopausal therapy, the doses of which are exponentially higher doses than those in residues of estradiol 17β present in beef.[18]) FDA concluded that estradiol 17β is not a genotoxic agent, and that any carcinogenic effects of estradiol 17β in experimental animals are a consequence of persistent overstimulation of the hormonal system. If consumption of residues of estradiol 17β in edible tissues of food-producing animals does not cause such persistent overstimulation of the hormonal system in humans, then FDA concludes that individuals consuming those residues will not be subject to an increased risk of cancer.

27. 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. FDA has concluded that for estradiol 17β (and its simple ester derivatives), human safety can be assured without the need for extensive toxicological testing in experimental animals. This is because the amount of estradiol 17β present in edible tissues of food-producing animals is very small relative to the endogenous production in humans. FDA has concluded that no physiological effect (or pathological effect, such as cancer) will occur from chronic ingestion of animal tissues that contain a residue level of estradiol 17β equal to 1% or less of the amount produced daily by the segment of the population with the lowest endogenous production (prepubertal boys). Based on this conclusion, FDA has set a safe concentration of 0.06 micrograms for estradiol 17β. To obtain FDA approval for drug intended for use in food animals that contains estradiol 17β, the drug's sponsor must demonstrate that residues of estradiol 17β in edible tissues from animals treated with that drug will not exceed the permitted increased exposure. This requirement has been satisfied for all of the veterinary drugs containing estradiol 17β that are approved by FDA for use as growth-promoting agents in cattle.

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?

28. For the US perspective on long-term human exposure to hormone residues in meat from treated cattle, please refer to our answer to Question 3 above.

29. For JECFA's approach for assessing the effects of long-term dietary exposure to hormone residues, please see the 52nd Report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series 893, pp. 57-60, 2000) as well as the information provided by Dr. Tritscher, JECFA Secretariat, at the Meeting with the Experts held in Geneva on 27-28 September 2006.

[18] *See* US Rebuttal Submission, fn. 72.

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?

30. At this stage of the proceedings, it is irrelevant whether or not the United States has determined that the EC's bans are or not WTO-inconsistent. The determination of whether or not the EC has brought its measures into conformity with DSB recommendations and rulings now rests with the Panel.

31. As noted in paragraphs 19-22 and Table 1 of the US Rebuttal Submission as well as in the US Oral Statement (Legal Issues, paragraphs 9-10) at the second substantive meeting with the Panel, the EC has produced materials related to its measures in a staggered, piecemeal fashion. The question of whether the United States is still "missing" information would perhaps be better suited for the EC, particularly in light of the fact that it attempted to produce evidence in support of its measures as recently as the meeting with the scientific experts.

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.

32. As noted in the US response to EC Question 1 (to the United States and Canada) above, JECFA completed a quantitative exposure assessment for each of the hormones at issue in these proceedings. The EC's insistence on highlighting the shortcomings of its own "risk assessment" by comparing its efforts to those of JECFA is therefore perplexing. The United States would also reiterate that there are several additional reasons for finding that the EC has failed to conduct a risk assessment, as appropriate to the circumstances, for estradiol 17β. These include failing to satisfy other steps (of the four) for completing a risk assessment and failing to support the scientific conclusions reached in its Opinions on scientific evidence. The United States has discussed these shortcomings in detail in its previous submissions to the Panel.

ANNEX C-5

COMMENTS BY THE UNITED STATES ON THE REPLIES OF THE EUROPEAN COMMUNITIES TO QUESTIONS POSED BY THE PANEL AFTER THE SECOND SUBSTANTIVE MEETING

(31 October 2006)

1. The United States appreciates this opportunity to provide comments on the 18 October 2006, "Replies to Questions from the Panel after the Second Substantive Meeting by European Communities" ("EC") to the 5 October 2006, additional questions from the Panel.

Questions to all the 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?

2. The EC's response to Question 1 reemphasizes several points raised in the US response to this question. In our response, we explained how what the EC refers to as EC's "systemic claims" are premised on the EC's view of how the *Understanding on Rules and Procedures Governing the Settlement of Disputes* ("DSU") should be rewritten rather than grounded in the actual text of the DSU. The EC's response highlights this fact. For example, the EC argues that "from the EC's 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." (Emphasis added). This statement is remarkable for several reasons.

3. First, rather than directing the Panel's attention to a specific obligation in the DSU which the United States has allegedly breached, the EC describes a claim based on the "EC's point of view" of what the DSU should provide for. As we have previously shown, the EC's point of view on the DSU does not equate with actual obligations of WTO Members under the DSU. Second, the EC relies on its theory of "presumed compliance", by which it believes that through a simple declaration of compliance it in turn satisfied its burden of proof as a complaining party in WTO dispute settlement. We have demonstrated in previous submissions that a declaration of compliance does not amount to "presumed compliance" for purposes of dispute settlement. Third, the EC argues that a US breach of these "procedural" or "systemic" obligations should be found "irrespective of the requirements of actual compliance." The EC's argument is untenable. A multilateral determination that the EC has complied with the Dispute Settlement Body's ("DSB's") recommendations and rulings in the *Hormones* dispute is an essential prerequisite to any finding of a US breach of its obligations under the DSU.

4. Finally, the EC again notes that "several Panels in the past have already ruled on Article 23 claims." The United States has provided detailed arguments relating to these earlier proceedings and demonstrated how they are inapt to the situation at hand.[1]

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 17ß as a growth promoting hormone to cattle, in particular in the United States' and

[1] *See*, *e.g.*, US Rebuttal Submission, paras. 6-8, 15-16.

Canada's markets? If so, please indicate where this assessment is to be found in the evidence provided to the Panel.

5. The EC's response to Question 4 is flawed for several reasons. Upon review of the materials put forward by the EC in support of its claim that good veterinary practices are not adhered to in the United States, it is clear that the EC has neither demonstrated the existence of such a risk, nor has it assessed the probability of the failure of good veterinary practices in the United States.

6. As noted by Canada in its response to Question 4, the EC appears to rely on a draft document (Exhibit EC-73) that purportedly assesses the "risk" arising from abusive use and difficulties of control of growth promoting hormones. The EC has not clarified the actual status of this draft document, and in its 1999 Opinion refers to it only briefly. This draft document and the 1999 and 2002 Opinions do not assess the risk of failure of controls or misuse in the United States for several reasons. We have already highlighted the most significant shortcomings in these materials in our previous submissions to the Panel.[2]

7. The EC claims to have demonstrated the "existence of a risk" of the failure to satisfy good veterinary practices in the United States. In support of this claim, the EC cites to several of its misuse studies, noting that the cited experiments "were carried [out] with hormonal implants that are actually licensed for use in the US and Canada and considered both their recommended use and situations of misuse and/or misuse." The United States has provided detailed arguments demonstrating that these misuse studies are not representative of the actual use of the six hormones at issue for growth promotion purposes in the United States. Rather, the studies portray unrealistic dosing scenarios, and only then demonstrate violative residue levels when animals are overdosed with numerous implants (stacking of implants). Dr. Boobis described these studies and clarified that they are not representative of realistic conditions nor do they in any way meaningfully assess a risk from misuse.[3]

8. Indeed, none of the experts (including Dr. De Brabander) pointed to any evidence presented by the EC of an actual risk from the misuse of the six hormones as growth promoters in cattle in the United States. Nor did any of the experts opine that the EC had actually assessed in a proper manner the likelihood that such a failure would occur.[4]

9. The EC also claims to have undertaken studies or provided evidence demonstrating the "level of risk" from "situations of abuse and/or misuse." However, none of the materials presented by the EC provide evidence of a risk of a failure of good veterinary practices, nor do they assess the risk that such a failure would occur. The United States has discussed this gap in the EC's case (including the EC's failure to satisfy the requirements of SPS Article 5.2) in detail.[5] In particular, we have noted the stark absence of any evaluation by the EC of the actual workings of the US food safety system, including oversight by federal inspectors and use of programs such as the National Residue Program to monitor the use of growth promoting hormones in the cattle industry, as would be required by SPS Article 5.2. We will not repeat those arguments here, but will instead highlight a few fundamental shortcomings in the EC's "assessment" of the potential for the failure of controls.

10. For instance, the EC's arguments relating to the existence of a risk of multiple dosing, or stacking of implants are misguided. The EC argues that there are economic incentives to misuse growth promoting hormones (*i.e.*, not abide by on-label instructions).[6] However, no such incentives

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[2] *See*, *e.g.*, US Rebuttal Submission, Section II.B.4.

[3] *See* Response of Dr. Boobis to Panel Question 62.

[4] *See* US Response to Panel Question 4 after the Second Substantive Meeting.

[5] *See*, *e.g.*, US Rebuttal Submission, Section II.B.4; US Comments on Responses of the Experts, paras. 101-112.

[6] *See*, *e.g.*, Exhibit EC-73, para. 22.

exist, as individual implants are marketed to provide optimal doses.[7] The EC's purported "evidence" of the risk for stacking of implants is the University of Nebraska Beef Cattle Update (Exhibit US-27), cited extensively in Exhibit EC-73.[8] However, as noted by the Update's author, Dr. Dee Griffin, the Nebraska Beef Cattle Update does not support the conclusion that stacking of implants is either a common or recommended practice in the United States. To the contrary, Dr. Griffin notes:

> Using more than a single implant at the same time has been termed "double implanting" or "stacking". Stacking implants, intentionally or unintentionally, has been known for decades to cause both gain and feed efficiency to be poorer than when FDA approved implants were used in accordance with the FDA approved label. ... Stacking would cost our beef producers $50 to $100 (USD) per animal in lower carcass value.

11. In other words, according to Dr. Griffin, "[u]se of FDA approved growth promotants other than as labeled is a costly mistake." This is why "beef production specialists in the USA never recommend simultaneous or double implant administration."[9] The EC also notes (in its answer to Question 12) that "multiple implanting of animals with these hormones is recommended by the manufacturers." However, the EC provides no evidence to support this statement. To the contrary, FDA approval of veterinary drugs includes the regulation of manufacturers' labels and none of the labels for the growth promoting hormones at issue recommend treatment with more than one implant at a time.[10]

12. The EC also cites to the results of its missions to the United States as "evidence" that there is a risk of failure of controls. The cited materials conclude that hormone implants were being illegally used in the US veal industry.[11] The EC contends that this illegal use of hormones in the veal industry is somehow evidence of a risk of failure of controls in all sectors of beef cattle production.[12] However, growth promoting hormones are not approved in the United States for use in cattle intended for the veal industry. Such use is illegal and any carcasses or meat products from veal calves treated with growth promoting hormones would be deemed to be "adulterated" and prohibited from sale in the United States and for export. Misuse in this sector of animal agriculture cannot be extrapolated to a completely separate sector (feedlot cattle) in which the use of growth promoting hormones is approved and a system of controls exists for their legal use. It is telling that the EC relies on anecdotal evidence from the veal industry in its attempt to cast aspersions on the efficacy of the US system of controls in feedlot cattle. The absence of evidence of misuse in feedlot cattle is testament to the effectiveness of controls in that industry. In any event, the United States took all necessary steps to deal with the problem of illegal use of implants in veal calves.

13. For example, upon discovery of the illegal use of growth promoting hormones in the veal industry, the United States Department of Agriculture's Food Safety and Inspection Service ("FSIS") published Notice 31-04: *Verification of implant usage in non-ruminating calves (i.e., veal calves),*

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[7] *See* Letter from Dr. Dee Griffin (Exhibit US-28).

[8] Exhibit EC-73, paras. 22 (fn. 35) and 47 (fn. 63), and fn. 37.

[9] Exhibit US-28 (emphasis added).

[10] For example, the manufacturer's label for Synovex Plus implants (estradiol plus trenbolone acetate; http://www.wyeth.com/products?product=/wyeth_html/home/products/animal_health/SYNOVEX%c2%ae%20Implants/prescribinginfo.html) states "DOSAGE: One implant (eight pellets), containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate, is administered to each steer or heifer by subcutaneous implantation in the middle one-third of the ear" and "DIRECTIONS: Implant complete contents of one cartridge cell per steer or heifer."

[11] *See*, *e.g.*, Exhibit EC-73, paras. 34-35; *see* EC Responses to Questions from the Panel After the Second Substantive Meeting, Question 4, paras. 15-16 and footnotes 4-5.

[12] *See* EC Responses to Questions from the Panel After the Second Substantive Meeting, Question 4, paras. 15-16 and footnotes 4-5.

providing instructions for inspection program personnel to use when they suspect the use of implants in non-ruminating calves. This direction to field personnel made clear that any non-ruminating (veal) calf presented for slaughter with an implant or on which there is evidence of implant use was to be condemned by USDA inspectors. USDA inspectors visually inspect veal calves (and feedlot cattle) for any signs of implant use during ante-mortem (pre-slaughter) and post-mortem (post-slaughter) inspection.

14. Additionally, on 16 July 2004, the US Food and Drug Administration ("FDA") and FSIS jointly issued a letter to the American Veal Industry, as well as to other trade associations, reiterating that the practice of implanting food animals that are to be marked as "veal" with growth promoting implants is illegal. Finally, in order to ensure that veal illegally treated with growth promoting hormones was not entering the US market or exported, FSIS included the testing of veal in its National Residue Program. There have been no positive samples found in either 2004 or 2005, a fact that is clear evidence of the effectiveness of FSIS/FDA's efforts to eradicate illegal use of hormones in this industry.

15. In sum, upon learning of an illegal use of growth promoting hormones in the veal industry, the FSIS and FDA took the necessary steps to stop this illegal use. These efforts are not evidence of a failure of controls in the feedlot cattle industry, for which the use of growth promoting hormones is approved. If anything, the anecdotal evidence of the illegal use of hormones in the US veal industry is evidence of the ability of the US food safety system to isolate and deal with any potential problems in order to ensure that meat sold domestically, as well as for export, complies with federal requirements.

16. Finally, the United States was surprised and disappointed to see that the EC has misquoted US arguments regarding the potential for the failure of controls. The EC ascribes the following statement to the United States: "[t]he US argues that 'no food safety system is safe,' implying that the other WTO members are obliged to accept the failures of the US system." To the contrary, what the United States actually said was that "[n]o food safety system is perfect." There is a vast difference between safety and perfection. The US food safety system is "safe" and we have demonstrated how our system functions effectively and protects consumers. In making the statement that no system is "perfect" at the second substantive meeting with the Panel, the United States was simply highlighting the fact that the EC has apparently developed a standard for good veterinary practices that would not tolerate any failures whatsoever – a virtual 100% assurance that controls would never fail. The EC's position is ironic in light of the fact that the EC cannot control its own black market for the use of growth promoting hormones in cattle resulting from its imposition of a ban on their use. In other words, despite its ban, the EC fails to meet the very standard it has set for good veterinary practices in these proceedings. If this unrealistic and impractical standard were to be adopted by all WTO or Codex members, countries would be able to ban the import of EC meat despite the EC's attempt to ban the use of growth promoting hormones.

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 17ß 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 17ß for growth promotion purposes?

17. In an attempt to justify the dosage of estradiol administered to rats in the study by Cavalieri *et al*. (Exhibit EC-125) as "not massively high", the EC notes in its response to Question 5 the imminent publication of an underlying study (Mailander *et al*.) which would supply additional information. The cited study has since been published and, contrary to the EC's claims, it does not provide information

about actual exposure of rats to estradiol following implantation. In fact, it is a completely different study, in which rats were not treated with estradiol but with estradiol-3,4-quinone, one of the catechol metabolites of estradiol. As the United States has pointed out in previous submissions, and as was confirmed by Dr. Boobis at the meeting with the experts, results obtained with the catechol metabolites of estradiol cannot be taken as evidence that estradiol will have the same effect *in vivo* (because it has not been established that the catechol metabolites form *in vivo* at concentrations high enough to cause deleterious effects). Therefore, the report referred to by the EC in its response to Question 5 (Mailander *et al*.) provides no additional information relevant to the study by Cavalieri *et al*. (Exhibit EC-125). The United States reiterates its criticisms of the Cavalieri *et al*. study, in which the dose of estradiol was so high that it resulted in the death of nearly one half of the rats. Such a dose is not relevant to the relatively minuscule amounts of estradiol found in beef from cattle treated with estradiol 17β for growth promotion purposes.

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)

18. As an initial matter, the United States is struck by the fact that the EC purports to be able to respond to the Panel's question without knowing what measure would be found inconsistent or what the precise basis for the finding of inconsistency would be under the hypothetical. The Panel in the question itself highlighted Article 19 of the DSU, which specifies the Panel's recommendation in the event of a finding of an inconsistency, and the EC is aware that the Member concerned retains the discretion on how to implement any such recommendation.

19. Consequently, the EC's response to Question 6 is rather revealing. First, the EC response is a telling snapshot of its overall failure to demonstrate that the United States has breached its obligations under the DSU by continuing to suspend concessions to the EC despite the EC's unilateral declaration of compliance. As a general matter, if the US suspension of concessions were a measure in breach of its WTO obligations, the United States would not be able to maintain them. However, the EC's reply indicates that the United States would be free to continue to apply the suspension of concessions and related obligations pending the outcome of an Article 21.5 proceeding.[13] The EC thus admits that even under its own theory, the US suspension of concessions is not inconsistent with the DSU. Furthermore, the EC thus admits that the suspension of concessions is not related to any "new" determination by the United States, in breach of Article 23 of the DSU, that the EC measures taken to comply are inconsistent with the covered agreements.

20. Second, the EC's reply confirms that the United States is not in breach of Article 21.5 of the DSU. For example, the EC argues that "there can be no doubt that the United States and Canada are

[13] *See* EC Responses to Questions from the Panel After the Second Substantive Meeting (Question 4), paras. 15-16.

under an obligation to withdraw the suspension of concessions . . . if they do not initiate a 21.5 proceeding." However, to date, the EC has failed to identify any specific obligation in the text of Article 21.5 that has allegedly been breached by the United States. The United States has noted this failure on several occasions.[14] It is therefore remarkable that the EC avers that "there can be no doubt that [the United States] [is] under an obligation to initiate a 21.5 proceeding." Rather than finding a basis for its claim in the text of Article 21.5, the EC's claim of a US breach is simply a product of its so-called "systemic" claims of a breach of the DSU which find no basis in the actual text of the DSU.[15]

21. As we have demonstrated, the United States would only be obligated to withdraw its application of the suspension of concessions upon a demonstration by the EC (as the complaining party) that it had satisfied one of the three conditions of DSU Article 22.8. The EC has failed to demonstrate that it has satisfied any of these conditions.

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 17 ß 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 17 ß?

(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.

22. In its response to Question 8, the EC again declares that "beyond doubt" it has "completed the four steps [of risk assessment]."[16] The EC also comments that "[t]he defending parties may disagree, but they cannot credibly argue that the European Communities has not completed the four steps of the risk assessment." Neither of these statements is grounded in the reality of this dispute, which includes consultation with scientific experts on the specific question of whether the EC has satisfied these very same four steps in its risk assessment for estradiol 17β. Not only can the United States "credibly

[14] *See*, *e.g.*, US First Written Submission, Section IV.D.3(a)(iii) (demonstrating, among other things, that Article 21.5 sets no deadline by which a party must seek recourse to dispute settlement; Article 21.5 does not obligate the original complaining Member to initiate a compliance proceeding; and Compliance with Article 21.5 may be achieved through recourse to other provisions of the DSU).

[15] *See* US First Written Submission, Section IV.D.3(a)(iii); US Answers to Panel Questions after the First Substantive Meeting, paras. 11, 16-17, 38-40; US Rebuttal Submission, paras. 5-12.

[16] Note that the EC apparently claims in paragraph 35 that it has conducted a risk assessment "for all these hormones." To date, the United States was not aware that the EC claimed to have satisfied its obligations under SPS Article 5.1 for the five provisionally banned hormones.

argue" that the EC has failed to satisfy the four steps, the Panel's scientific experts have confirmed that the EC has not satisfied each of the four steps.[17]

23. In its attempt to demonstrate that it has completed a risk assessment for estradiol, the EC cites to section 4.1.5 of its 1999 Opinion in which it concludes that "the FDA's acceptable daily intake (102 ng/per person/day) could exceed the daily production rate of oestradiol by 1,700 fold (of pre-pubertal children)." Taking the low bioavailability of estradiol into account and assuming the metabolic clearance rate of estradiol in children is one half that of adults, the EC then adjusts its "quantitative" estimate and concludes that "the FDA acceptable daily intake could still be 85 fold too high." These statements are incorrect and unsupported by scientific evidence or mathematical analysis.

24. First, the FDA has never set an acceptable daily intake (ADI) for estradiol. Instead, as explained in FDA Guidance for Industry No. 3,[18] for endogenous sex steroids like estradiol, FDA sets a permitted increased exposure based on daily production of each steroid in the segment of the human population that synthesizes the least amount (prepubertal boys in the case of estradiol).

25. Second, the EC's exposure calculations rely on results of the Klein assay (1994), which indicated that blood levels of estradiol in prepubertal boys were 100-fold lower than previously reported. The United States has demonstrated the flaws of the Klein assay on several occasions[19] and the validity of this 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, the EC has not established the magnitude of the difference, and there was certainly no agreement among the experts on the 100-fold difference cited by the EC. The EC itself recognized the inaccuracy of the Klein assay results in its Comments on the Replies by the Panel Experts (Question 38).[20] Equally as speculative in the EC's exposure calculation is the assumption that the metabolic clearance rate of estradiol in children is one-half that of adults. No scientific data have been presented to support this assumption.

26. Third, the EC's exposure calculations are flawed because they use U.S.-permitted incremental increases[21] to estimate actual daily exposure to estradiol from eating beef. These permitted incremental increases are levels of residues that are permitted in excess of increments above the concentrations of estradiol naturally present in untreated animals; they do not represent actual amounts of estradiol found in edible tissues. Therefore, use of these numbers to derive an "acceptable daily intake" of 102 ng/person/day is factually incorrect. As the United States has stated previously, a more accurate (and still very conservative) estimate of excess daily intake of total estrogens from eating beef from treated animals – 30-50 ng/person/day, *i.e.*, one third to one half of the EC's

[17] US Comments on the Responses of the Scientific Experts, paras. 18-32; *see also* US Oral Statement (Expert Issues) at the Second Substantive Meeting, paras. 18-20.

[18] FDA Guidance for Industry No. 3: General principles for evaluating the safety of compounds used in food-producing animals. http://www.fda.gov/cvm/Guidance/GFI003.pdf.

[19] *See*, *e.g.*, US First Written Submission, paras. 84 (and footnote 92) and 159; US Rebuttal Submission, para. 44.

[20] Responding to Dr. Boobis' criticisms of the Klein assay, the EC stated "[t]he real values for serum 17β -oestradiol in prepubertal children still remain to be properly documented."

[21] For veterinary drugs that occur naturally in animals, like estradiol, FDA does not set tolerances or maximum residue limits. Instead, FDA establishes levels of residues that are permitted in excess of increments above the concentrations of estradiol naturally present in untreated animals. *See* 21 CFR § 556.240.

erroneous estimate of 102 ng/person/day – can be found in the residue monograph from the 52nd JECFA meeting.[22]

27. In other words, the paragraph cited by the EC is replete with inaccuracies and conclusions that are unsupported by scientific evidence, and does not support the conclusion that the EC has, in fact, completed a risk assessment for estradiol. In any event, there are numerous other reasons for concluding that the EC has failed to do so. We have highlighted these in our previous submissions and several of these shortcomings have been discussed by the scientific experts.

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)?

28. In its response to Question 9, the EC defines "mere doubt" as "not any kind of doubt but doubt that is scientifically established." The United States has not been able to locate, let alone find a definition of, the term "mere doubt" in any scientific materials, the SPS Agreement, or WTO dispute panel or Appellate Body guidance. The EC appears to have invented this term during the course of these proceedings, and now hopes to have its measures analyzed against the backdrop of this fictitious (and self-defined) standard. This is an untenable position and should be disregarded as such. In any event, pursuant to the EC's own definition, a "mere doubt" must be a "scientifically justified" doubt. The EC has failed to present any evidence that there is scientifically-justified doubt about the safety of any of the six hormones when used for growth promotion purposes in cattle. Therefore, the EC has failed to satisfy its own standard.

Q11. What is meant by no "additive risk"? Please explain to which "risks" these are "additive".

29. In its response to Question 11, the EC states that "[i]t 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." To the contrary, in the course of these proceedings the United States has never argued that endogenous hormones can cause or promote cancer. Nor has the EC presented any convincing evidence that this is so. It is overly simplistic and unscientific to say that endogenous hormones are "sufficient" to cause cancer, and the EC's response to Question 11 appears to be nothing more than an attempt to attribute statements to the United States and Canada that they have never made. Furthermore, the EC has failed to present evidence that there is any "additive" risk from the consumption of meat from cattle treated with any of the six hormones for growth promotion purposes.

30. For example, the EC relies on the 10th and 11th Reports on Carcinogens in support of its contention that consumption of estradiol residues in meat from treated cattle will be "additive" to the risk of cancer from existing (endogenous) exposure and exposure from naturally-occurring sources of estradiol. However, the EC is incorrect when it concludes that veterinary use of steroidal estrogens in food animals can increase estrogens in edible tissues to levels "in general substantially higher than the normal (endogenously produced) levels." As demonstrated by the United States in response to Question 1 from the EC following the Second Substantive Meeting, the EC's own exhibits (Exhibits EC-34 and 51A) clearly indicate that the increase in estradiol residues in muscle of treated cattle is usually small (1.1 to 2.3-fold) and that it was only detectable in some of the treated animals. Moreover, these increases result in residue levels that are within the range of naturally-occurring

[22] *See* "Evaluation of certain veterinary drug residues in food", Fifty-Second Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series: 893 (2000) ("52nd JECFA Report"). FAO Food and Nutrition Paper 41/12. (Exhibit US-5). www.fao.org/ag/agn/jecfa/archive_en.stm.

concentrations. Therefore, the statement that levels of estradiol in meat from treated cattle are "substantially higher than the normal (endogenously produced) levels" is grossly inaccurate.

31. Rather than citing to Exhibits EC-34 and 51A (some of the EC's more recent data that show a small and in certain cases undetectable increase in residue levels), the EC refers instead to Table 2 of its 1999 Opinion in its attempt to show that the residue level increase is "substantial." However, some of the data in Table 2 refer to veal calves and bulls, neither of which are relevant to this dispute.[23] Further, neither the source nor the date of these data is indicated in Table 2. It is therefore not possible to evaluate the validity of these data or, more importantly, whether they accurately represent the average increase in estradiol residues in treated cattle (versus the most extreme cases).

Q12. A 1999 Report of the Committee for Veterinary Medicinal Products of the European Communities refers to the low bioavailability of oestradiol 17ß. 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)

32. The EC disagrees with the US statement that to overcome the low bioavailability of estradiol, very large amounts of the hormone must be administered orally. However, rather than citing to any number of review articles available on this subject,[24] the EC relies instead on a single pilot study in girls with central precocious puberty (Exhibit EC-99). In this study, girls with central precocious puberty were administered estradiol orally to overcome the growth inhibition associated with GnRH agonist therapy. The authors determined that a "mini-dose" of 8 micrograms (versus the adult dose of 625 micrograms) of conjugated equine estrogen was sufficient to stimulate growth. The United States does not disagree that 8 micrograms is a low dose compared to 625 micrograms, nor does it disagree that this dose was orally bioactive in these patients. However, the relevant fact is that 8 micrograms of estrogen is exponentially greater than the amount of estradiol or its metabolites found in a serving of beef from treated cattle.[25]

33. In addition, the EC states that JECFA, and by extension the 1999 CVMP Opinion, 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 statement is, at least in part, factually incorrect. The residue monograph of the 52nd JECFA Meeting contains 23 tables describing concentrations of estrone in edible tissues from both untreated and treated cattle. Theoretical daily intakes were calculated and clearly presented for estrone alone, estradiol alone, and estrone and estradiol together ("total estrogens").

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[23] The use of growth-promoting hormones in veal calves is not approved in the United States. Relative to all beef cattle, the United States slaughters very few bulls for meat and there is no reason to implant these animals with hormones to promote growth. Ironically, in contrast, the EC regularly slaughters bulls for human consumption, the meat from which may have endogenous testosterone levels much greater than that from steers (castrated male cattle) to which hormones have been administered for growth promotion purposes according to good veterinary practice. *See* US First Written Submission, para. 52, citing Eurostat data regarding meat production in the EU-15 (in which meat category v12 (bulls) comprises approximately 29.5% of total cattle slaughtered in the region). (Exhibit US-8). In contrast, less than 2% of cattle slaughtered in the US are bulls while approximately 50% are steers (castrated male cattle).

[24] For example, Fotherby K. Bioavailability of orally administered sex steroids used in oral contraception and hormone replacement therapy. Contraception 1996; 54: 59-69.

[25] The difference between the dose of estrogen used in Exhibit EC-99 and the amount in beef is difficult to quantify precisely because conjugated equine estrogen, not estradiol, was used in the study. Equine estrogens are mixtures of several estrogen sulphates which, unlike estradiol, are water soluble. Therefore, conjugated equine estrogens are believed to have a greater oral bioavailability than estradiol. *See* footnote 19 above (Fotherby).

34. Further, data in Exhibit EC-49 indicate that treatment of cattle with a single implant containing estradiol may result in increased concentrations of lipoidal estrogens in fat and liver, but not muscle or kidney; however, the data are difficult to interpret. In Exhibit EC-51A, the authors concluded that "estradiol-17β-17-esters assayed at significant concentrations in fat from 5 ppt in control to more than 100 ppt in 4-doses (sic) implanted animals. Curiously, mean concentrations of estradiol-17β-17-esters in liver were not significantly modified by the implantation treatment." These observations indicate that lipoidal estrogens are relevant only for fat and not the other edible tissues. Most importantly, the EC has not provided any scientific evidence indicating that consumption of lipoidal estrogens in meat from treated cattle results in a health risk to the human consumer.

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)

35. The United States notes that the EC agrees that the two lists setting out its "17 Studies" are substantively different. The EC describes this difference as the result of "further publications of partial aspects of the studies." Not only is this excuse unclear, it is patently insufficient. Either the EC provided the United States with the necessary materials at the outset of these proceedings (when the United States filed its request under Article 5.8 of the SPS Agreement), or it did not. The EC's response to Question 16 makes clear that the list of studies provided to the United States at that time (*i.e.*, the list attached to the 2002 Opinion at the outset of these proceedings) is different than the list put forward by the EC in the course of these proceedings.

36. Also, the United States notes that the EC relies heavily on its Exhibit EC-65 (a book of studies) in support of its argument that the United States was in possession of all of the necessary materials comprising the "17 Studies." However, Exhibit EC-65, along with numerous other scientific documents, was only filed by the EC with its Rebuttal Submission (in other words, at the same time as the US Rebuttal Submission and Table 1 thereto). In addition, there are still gaps in the EC's attempt to reconcile its production of evidence with Table 1 to the US Rebuttal Submission. For example, regarding Study Ten, the EC notes that "[t]his study was not yet published as research continued after 2002. It appears that it has not been published yet." (*See* Exhibit EC-129).