UNITED STATES – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE (WT/DS320)

COMMENTS OF THE UNITED STATES ON THE COMMENTS OF THE EUROPEAN COMMUNITIES ON THE RESPONSES OF THE SCIENTIFIC EXPERTS

July 12, 2006

A. Introduction

1. The United States appreciates this opportunity to provide comments on the comments of the European Communities ("EC") on the responses received from the six scientific experts and the three international organizations selected by the Panel. The United States will first provide general comments on the EC's comments and then provide specific remarks on individual comments offered by the EC on the experts' and international organizations' responses.

B. General Comments

1. Qualifications of experts

2. In several of its comments, the EC questions the credibility of two of the scientific experts selected by the Panel, Drs. Boobis and Boisseau, and seeks to dismiss their responses based on an alleged lack of qualification rather than a lack of scientific foundation or basis in the experts' responses themselves. The United States notes that Drs. Boobis and Boisseau are more than qualified to provide advice to the Panel on the subject matter at issue, the safety of meat and meat products from cattle treated with hormones for growth promotion purposes. This is evidenced by the high quality of their responses to the Panel's questions, their extensive *curriculum vitae*, their nomination by the Codex Alimentarius Commission ("Codex") and the Joint FAO/WHO Expert Committee on Food Additives ("JECFA") to serve in the expert group, and the Panel's ultimate choice to seek their advice as members of the expert group. This is also evidenced by the fact that the EC only seeks to impugn the qualifications of the experts in scenarios where it has concluded their responses are not favorable to its arguments.[1]

3. In addition to seeking to dismiss expert opinions based on an alleged lack of qualification, the EC also attempts to discard Dr. Boisseau's responses to certain questions based

[1] *See*, *e.g.*, EC Comments on the Experts' Responses (Questions 37 and 44), where the EC offers the opinion of Dr. Boisseau, without qualification, in support of its position. Contrast to EC Comments on Panel Question 2, where the EC notes, "[a]s the EC has pointed out during the selection procedure, Dr. Boisseau does not possess any expertise on these substances, as he does not appear to have carried out any specific research on these substances during his professional life." EC Comments on the Experts' Responses (Question 2), p. 2.

on the fact that he initially informed the Panel that he may not be in a position to respond to those questions. The fact that Dr. Boisseau was unsure as to his ability to respond to certain questions is not a valid reason for ignoring his ultimate responses to these questions. Indeed, Dr. Boisseau's responses appear to be very well-researched, and he has clearly put a great deal of effort into providing the Panel sound advice on these issues. Further, the United States notes that this is another example of the EC attempting to impugn the qualifications of an expert only where that expert has offered answers or points of view that do not support the EC's arguments. For example, the EC does not raise similar concerns regarding Dr. De Brabander's responses to Panel Questions 44-48 and 50-51 despite the fact that Dr. De Brabander, in an April 24, 2006 e-mail to the Panel noted, "I am an analytical chemist so I could only provide adequate answers to questions on residue analysis. That means Db question [2]7-35 and f question 49."[2] Despite this statement delimiting his experience to residue analysis, Dr. De Brabander offers several responses on an entirely unrelated category: good veterinary practices in the United States and Canada.

2. Scope of experts' responses and legal obligations under the SPS Agreement

4. As previously noted by the United States in its comments on the experts' responses, the role of the scientific experts is a narrow one of providing a panel information, advice and opinions on certain aspects of the matter that is the subject of a dispute.[3] Despite this fact, the EC has, in several of its comments, complained that the experts should have tempered their responses based on what the EC believes are Members' legal obligations under the *Agreement on the Application of Sanitary and Phytosanitary Measures* ("SPS Agreement"). For instance, in its comments on the experts' responses to Panel Question 5, the EC argues, "the answers of all scientists do not take into account the legal requirements of the SPS Agreement in this area, as interpreted by the Appellate Body."[4] There is no reason that the experts should have taken these requirements into account. Indeed, their mandate is to provide the Panel with information and advice on scientific and technical issues, not to make legal judgments regarding Members' measures, such as whether a measure is based on a risk assessment or satisfies the conditions for a provisional measure within the meaning of the SPS Agreement. Such judgments are reserved for the Panel.

5. In addition to confusing the role of experts in offering scientific advice to the Panel, the EC also notes in its comments that several of the Panel's questions concern aspects of risk assessment that are "not legally binding" since they are not referenced in the text of the SPS

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[2] E-mail of Dr. Hubert De Brabander to the Panel, April 24, 2006. (Emphasis added).

[3] *See* U.S. Comments on the Experts' Responses, Section B. *See also Agreement on the Applications of Sanitary and Phytosanitary Measures*, Article 11.2; *Understanding on Rules and Procedures Governing the Settlement of Disputes*, Article 13.

[4] EC Comments on the Experts' Responses (Question 5), p. 4. (Emphasis in original).

Agreement.[5] The EC appears to propose a very broad definition of what constitutes a risk assessment within the meaning of Article 5.1 of the SPS Agreement. Rather than accepting that guidance from international organizations such as JECFA and Codex provides important benchmarks for conducting a risk assessment and for objectively evaluating whether a Member's risk assessment has engaged in an adequate analysis of a risk, the EC instead proposes a notion of risk assessment devoid of any apparent form. The EC's concept of what is or is not a risk assessment ignores the text of Article 5.1, which states:

> Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life and health, taking into account risk assessment techniques developed by the relevant international organizations.[6]

6. The experts' responses clarify that there are abundant examples of risk assessment techniques developed by international organizations.[7] Indeed, the original *Hormones* panel concluded that "even though no formal decision has as yet been taken by Codex with respect to [sanitary] risk assessment techniques, Codex, and more particularly JECFA, has a long-standing practice with respect to the assessment of risks related to veterinary drug residues (including hormone residues)."[8] Such an assessment "consists of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization."[9] The EC reiterates this conventional four-step risk assessment procedure in its 1999 Opinion.[10]

7. The EC further attempts to blur the notion of what constitutes an appropriate risk assessment for purposes of the SPS Agreement by repeatedly noting that the Appellate Body has concluded that risk assessments may be either quantitative or qualitative. However, the EC's description of the Appellate Body's conclusions is overly simplistic. Rather than finding, as the EC appears to argue, that Members may simply conduct a qualitative risk assessment that is

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[5] *See*, *e.g.*, EC Comments on the Experts' Responses (Questions 4 and 6).

[6] SPS Agreement, Article 5.1. (Emphasis added).

[7] *See*, *e.g.*, Responses to Questions from the Panel of Dr. Alan Boobis ("Dr. Boobis Responses") (Questions 3 and 4), pp. 10-11.

[8] Panel Report, *EC – Measures Concerning Meat and Meat Products (Hormones)*, adopted on 13 February 1998, WT/DS26/R ("Panel Report"), para. 8.103.

[9] Panel Report, para. 8.103.

[10] *See* "Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health – Assessment of Potential Risks to Human Health from Hormone Residues in Bovine Meat and Meat Products", 30 April 1999 ("1999 Opinion"), p. 70. (Exhibit US-4).

devoid of any structure, necessary form or scientific rigor,[11] the Appellate Body simply determined that there is no requirement that a risk assessment establish a minimum quantifiable magnitude or threshold level of degree of risk.[12]

8. In conclusion, the EC's interpretation is not supported by the text of Article 5.1, cited above (either form of risk assessment must "tak[e] into account risk assessment techniques developed by the relevant international organizations"), nor is it bolstered by the responses of the experts, nor is it supported by the conclusions reached by the Appellate Body. To the contrary, the experts agree that qualitative risk assessments include the same core elements as quantitative risk assessments, save for some disagreement as to whether this includes a dose-response assessment in the hazard characterization (second step) step of risk assessment.[13] Further, regardless of whether a risk assessment is qualitative or quantitative, the scientific conclusions set out in the assessment must actually be supported by the underpinning scientific evidence cited in the assessment.[14] The EC has failed to demonstrate that it has accomplished this goal and the experts' responses confirm that it has not.

3. Responses of the international organizations are not "adequate and legally sound"

9. The United States believes that the responses of the international organizations speak for themselves, and that there is therefore no need to provide specific comments on these responses at this point. The United States has provided specific comments on the international organization responses, where appropriate, in its June 30, 2006 submission. The EC has presented no evidence to discount any of the conclusions reached by the international organizations. The EC has, however, alleged in a general comment that the responses from the international organizations are not "adequate and legally sound." The United States notes that the EC has provided no evidence in support of this speculation or purported standard, and that the input of these organizations, and similar international standard setting bodies has been sought in other SPS disputes, including the original *Hormones* dispute. Indeed, where a dispute involves the analysis of a Member's measure that diverges from relevant international standards (such as here), it is perfectly comprehensible why a panel would proceed with its evaluation by seeking input from international organizations.

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[11] *See*, *e.g.*, EC Comments on the Experts' Responses (Question 16).

[12] Appellate Body Report, *EC – Measures Concerning Meat and Meat Products (Hormones)*, adopted on 13 February 1998, WT/DS26/AB/R ("Appellate Body Report"), paras. 186, 253(j).

[13] *See* Responses of the Experts' to Panel Question 11.

[14] *See* Panel Report, *Japan – Measures Affecting the Importation of Apples: Recourse to Article 21.5 of the DSU by the United States*, WT/DS245/RW, adopted July 20, 2005, paras. 8.145-8.146 ("Japan – Apples (21.5)") (finding that "[s]ince the scientific evidence relied upon by Japan does not support the conclusions reached by Japan in its 2004 PRA, we conclude that the 2004 PRA is not an assessment, as appropriate to the circumstances, of the risks to plant life or health, within the meaning of Article 5.1 of the SPS Agreement.")

C. Specific comments on experts' responses

10. Question 1: The EC proposes several changes to Dr. Boisseau's response that are unsupported by scientific evidence. For example, the EC attempts to insinuate misuse scenarios (implant into animal's dewlap[15]; new recommendations for use of trenbolone acetate[16]) into the basic definitions of the hormones. In addition, the EC notes that "Dr. Boisseau's reply does not consider any progress in toxicological knowledge concerning these hormones, and in particular estradiol, since the 70th and 80th JECFA reports." However, the last meeting of JECFA was the 67th.[17] The "70th and 80th" JECFA reports do not exist, so it is unclear how Dr. Boisseau could have possibly taken their findings into account. The EC provides no comments on the response of Dr. Boobis, who has drafted detailed and well-documented definitions for the six hormones.[18] The United States notes that none of the experts' responses appear to alter the basic definitions of the six hormones relied on by the original *Hormones* panel.[19]

11. Question 2: The EC attempts to dismiss Dr. Boisseau's comments based on its view of his qualifications. The EC provides no scientific evidence or argument that discounts Dr. Boisseau's advice.[20]

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[15] In a production setting, placing an implant into the dewlap (hanging fold of skin under the neck) would be highly impractical and potentially dangerous to the handler. It would also likely result in slower, less effective absorption of the hormone due to the fatty tissue in the dewlap (versus the ear, which contains very little fat and is highly vascularized resulting in rapid and effective absorption of hormone from the implant). The suggestion that implants are deliberately misplaced into the dewlap appears to be speculation.

[16] The United States is unaware of any new recommendations for trenbolone acetate use and would be interested in the EC's source of this information. It is true that periodic reimplantation of cattle with growth promoting implants is common practice. This is done because each implant has a finite "payout period" during which the implant releases enough hormone to stimulate growth. The timing of reimplantation is carefully scheduled to maintain an effective concentration of hormone in the animal. It should be emphasized that reimplantation of cattle, because it is done near the end of the implant payout period, does not result in concentrations of growth-promoting hormones in meat that exceed the tolerances or MRLs.

[17] 67th Meeting, June 20-29, 2006 (Rome) (http://www.who.int/ipcs/food/jecfa/data/en/index.html).

[18] *See* Dr. Boobis Responses (Question 1), pp. 1-5.

[19] *See*, *e.g.*, Panel Report, paras. 2.6-2.9.

[20] *See* Section B.1 above.

12. Question 3: Contrary to the EC's suggestion, the experts and international organizations confirm that there are numerous international documents and guidance materials relevant to the assessment of veterinary drugs in food.[21]

13. The EC tries to dismiss as irrelevant the work on the hormones conducted by the Committee on Veterinary Medicinal Products ("CVMP") and the conclusions reached by that body to the analysis at hand. However, as noted by the United States in its Rebuttal Submission and confirmed by the experts' responses, the CVMP analysis of estradiol 17β and progesterone indicates that it was concerned primarily with hazards and risks arising from exogenous exposure of consumers to hormones and the possible need, in light of recent data, to perform new risk assessments for estradiol and progesterone.[22]

14. The CVMP concluded that new risk assessments for estradiol 17β and progesterone were not necessary and that certain residue levels of the hormones are safe based on some very basic conclusions on these hormones (*e.g.*, lack of genotoxicity, carcinogenic action only after prolonged exposure at high exposure levels) which contradict fundamental – but unsupported – conclusions set out in the EC's Opinions. It should be emphasized that the basic scientific information considered by the CVMP with respect to the risks of therapeutic and zootechnical use of hormones was the same information used by the SCVPH to assess the risks of hormones used for growth promotion, but the CVMP and SCVPH reached very different conclusions. Thus the CVMP evaluation is indeed relevant to this dispute and an analysis of the EC's Opinions, despite the EC's attempts to distance itself from the evaluation.[23]

15. Question 4: The EC dismisses the responses of two of the scientific experts (Drs. Boisseau and Boobis) and the international organizations by arguing that their responses are not limited to "legally binding" assessment techniques within the meaning of the SPS Agreement.[24] As noted above, it is not appropriate for the experts to comment on the legal nature of any aspect of the dispute. Further, the EC simply avers that the relevant guidelines or principles cited by

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[21] *See* U.S. Comments on the Experts' Responses, para. 13, citing Codex Responses to Questions from the Panel ("Codex Responses") (Questions 3 and 4), pp. 4-5; JECFA Responses to Questions from the Panel ("JECFA Responses") (Question 3), pp. 2-3; Dr. Boobis Responses (Question 3), pp. 10-11.

[22] *See* U.S. Rebuttal Submission, fn. 57. *See* Responses to Questions from the Panel of Dr. Jacques Boisseau ("Dr. Boisseau Responses") (Question 13), pp. 9-11; Dr. Boobis Responses (Question 12), p. 17.

[23] *See* "Report of the CVMP on the Safety Evaluation of Steroidal Sex Hormones in particular for 17β-Oestradiol, Progesterone, Alternogest, Flugestone acetate and Norgestomet in the Light of New Data/Information made available by the European Commission", Committee for Veterinary Medicinal Products (EMEA/CVMP/885/99) ("1999 CVMP Report"), p. 11 ("General Considerations") (Exhibit US-13).

[24] As noted in Section B.2 above, the experts are not in a position to determine what is or is not "legally binding" for purposes of the SPS Agreement. While experts' advice and responses may be discounted because, *e.g.*, they lack a scientific foundation or are not based on scientific evidence, they may not be summarily dismissed because a party believes that they touch on topics that are not "legally binding."

the experts are not "legally binding" for purposes of analysis of a measure under the SPS Agreement, without providing an explanation of why this is so. Contrary to the EC's suggestion, the responses of Drs. Boisseau and Boobis, JECFA and Codex indicate that there are in fact "risk assessment techniques developed by the relevant international organizations" within the meaning of Article 5.1 of the SPS Agreement that are pertinent to an analysis of the EC's Opinions, in particular to an analysis of whether the EC has conducted a risk assessment for the permanently-banned hormone, estradiol 17β.[25] Indeed, the EC itself has recognized this fact.[26] In addition, the EC provides no explanation to support its allegation that its risk analysis techniques are "much more advanced than JECFA" nor does it explain what relevance, if any, this conclusion has to these proceedings.

16. Question 5: The EC claims that the experts' responses "do not take into account the legal requirements of the SPS Agreement." As noted above, it is not appropriate for the experts to comment on the legal nature of any aspect of the dispute. In addition, the EC attempts to contradict the experts' responses with its own opinion, which appears to be of little relevance to the Panel's question, of how Codex and JECFA interact but provides no evidence to support this opinion.[27]

17. Question 6: The EC dismisses the responses of the scientific experts and international organizations by arguing that these responses are not limited to "legally binding" risk assessment

[25] *See* Dr. Boobis Responses (Question 4), p. 11 ("[T]here are guiding principles [for risk assessment] in place, that have been in existence since before 1999." "Specific guidance was [] developed by JECFA and adopted by Codex."); Responses to Questions from the Panel of Dr. Jacques Boisseau ("Dr. Boisseau Responses") (Question 4), p. 2 (The rationale for risk assessment "has been internationally harmonised through scientific conferences and it is possible to say that there was an international non written agreement on this rationale."); JECFA Responses to Questions from the Panel ("JECFA Responses") (Question 4), p. 2 (citing back to its answer to Panel Question 3, in response to which it provide numerous citations to guidance on risk assessment techniques); Codex Responses to Questions from the Panel (Question 4), p. 5. *See* Panel Report, para. 8.103.

[26] *See* 1999 Opinion, p. 70. ("Executive Summary") ("Conventionally, risk assessment is structured to address independently the intrinsic properties of the compound under consideration (hazard identification), the evaluation of the nature of effects in terms of a dose-response relationship (hazard characterization), the estimate of the dose/concentration of a compound in the daily diet (exposure assessment) resulting in the incidence and severity of potential adverse effects.") This final evaluation would be what is generally referred to as "risk characterization." (Exhibit US-4). This is further evidenced by the fact that the EC has argued in these proceedings that it has completed the four steps of a risk assessment. See EC Comments on the Experts' Responses (Question 14) ("it is obvious that [the SCVPH] has followed the four steps of risk assessment when it carried out its qualitative risk assessment.")

[27] *See* EC Comments on the Experts' Responses (Question 5), p. 4 (in which the EC opines, without evidentiary support, that "[i]ndeed, JECFA's reports and monographs are drafted in such a way as to leave practically no room to the members of the Codex Alimentarius Commission to decide on the appropriate level of health protection and the risk management options that are available to its members.")

techniques within the meaning of the SPS Agreement.[28] The EC simply avers that the relevant guidelines or principles cited by the experts are not "legally binding" for purposes of analysis of a measure under the SPS Agreement, without providing an explanation of why this is so other than an inapt citation to the *Hormones* Appellate Body Report discussing the distinction between "risk assessment" and "risk management." Contrary to the EC's suggestion, the experts (Drs. Boisseau, Boobis and Guttenplan) and JECFA confirm that there are four internationally-recognized steps to a risk assessment (hazard identification; hazard characterization; exposure assessment; risk characterization) and that these steps are in fact "risk assessment techniques developed by the relevant international organizations" within the meaning of Article 5.1 of the SPS Agreement that are pertinent to an analysis of the EC's Opinions, in particular to an analysis of whether the EC has conducted a risk assessment for the permanently-banned hormone, estradiol 17β.[29] In addition, the EC's comments appear to ignore the several conditions imposed on risk assessments by, *e.g.*, Articles 5.2 and 5.3 of the SPS Agreement.

18. The EC also notes that Drs. Boobis and Boisseau have "discard[ed] the relevance of some residues that are not pharmacologically active but may interfere with normal metabolic functioning of cells given their intrinsic chemical potential to form covalent adducts to biomolecules." However, it is unclear which residues the EC is referring to and the EC provides no scientific evidence indicating that such protein adducts actually: (1) form in vivo following consumption of beef from cattle treated with growth-promoting hormones, or (2) interfere with metabolic functioning of cells.

19. Question 7: The EC disagrees with the experts' responses because, according to the EC, "the accumulation of so much new peer-reviewed evidence since 1999 establishes clearly that oestradiol-17β is a direct carcinogen and does not act only through hormonal receptors." This appears to be the EC's opinion alone. Despite having reviewed the materials relied on by the EC in drafting its Opinions and the several other studies put forward by the EC in defense of its permanent ban on estradiol 17β, the experts do not share the EC's conclusion on the "clear" carcinogenic action of estradiol 17β.[30]

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[28] As noted in Section B.2 above, the experts are not in a position to determine what is, or is not "legally binding" for purposes of the SPS Agreement.

[29] Recall that the form of the EC's "risk assessment" (Articles 5.1 and 5.2 and Annex A, paragraph 4 of the SPS Agreement) is but one element of the analysis of the EC's measure (permanent ban on meat and meat products from cattle treated with estradiol 17β for growth promotion purposes). The United States has also argued that the EC's ban is not sufficiently warranted or reasonably supported by the EC's "risk assessment", and is therefore not "based" on a risk assessment, as appropriate to the circumstances, within the meaning of Articles 5.1 and 5.2 of the SPS Agreement. *See also* Panel Report, para. 8.103.

[30] *See*, e.g., Experts' Responses to Questions 13 and 16-18. The United States notes that the EC cites to several studies which were not previously submitted to the Panel in support of its comments in Question 7 ("[a] number of publications, some of which have been submitted by the [EC] to this Panel, have explored the threshold concept and the activity of hormones at very low doses.") The United States notes that these proceedings are well beyond the deadline for submission of "new" scientific evidence.

20. The EC cites to a study by Bhat *et al*. (not cited in the EC's Opinions) as demonstrating "the necessary role of catechols of estradiol . . . in induction of oxidative stress to induce tumors." However, review of the Bhat study reveals that it did not identify catechol estrogens as the cause of tumor formation; in fact, catechol estrogens are not even measured in the study. Instead, the Bhat study demonstrates that tumor formation in the Syrian hamster kidney following treatment with estradiol 17β is associated with oxidative stress. Although oxidative stress can be generated by metabolic recycling between catechol estrogens and their corresponding quinones, it is not unique to catechol estrogens and occurs in a variety of cell types in response to numerous natural and xenobiotic stimuli. Therefore, the Bhat study does not provide direct evidence of the "necessary role of catechols" in tumorigenesis in the Syrian hamster kidney.

21. Further, the Bhat study involves the treatment of hamsters with high levels of estradiol 17β for an extended period of time (7 months). Therefore, the possibility that estradiol 17β stimulated the growth of tumors via receptor-mediated, hormonal effects cannot be ruled out. In fact, Bhat recognizes this possibility, concluding, "[t]he hormonal effects of estrogens may promote the development of tumors." Finally, it is well-documented that the Syrian hamster kidney is particularly susceptible to estrogen-induced kidney tumors due to a species-specific shift in the pattern of estradiol 17β metabolism to favor production of 4-OH catechol estrogen.[31] Therefore, whether this model is appropriate to study potential effects of estradiol 17β from dietary sources on human health is very questionable.[32]

22. Question 8: The EC contrasts the experts' advice against its own unsupported scientific conclusions. For instance, the EC complains that "the evidence used by JECFA in the evaluation of these hormones is too old (dating from the 1970s) and has been obtained with outdated detection methods [*sic*] to be relevant today." This blanket conclusion is simply incorrect. For instance, JECFA based its conclusion to set ADIs for estradiol 17β, progesterone and testosterone on "[s]ufficient new data from observations in humans . . . which were suitable to

[31] This point appears to be confirmed by Dr. Guttenplan, who notes that there is only one animal model "that is well characterized and this is in the hamster kidney. As kidney is not a known target of estradiol in humans the extrapolation to humans is uncertain." Responses to Questions from the Panel of Dr. Joseph Guttenplan ("Dr. Guttenplan Responses") (Question 14), p. 4. (Emphasis added)

[32] The EC also cites to two papers by Russo *et al*., neither of which stand for the conclusion drawn from the papers by the EC. The first paper, Russo *et al*., *Estradiol is carcinogenic in human breast epithelial cells*, was: (1) performed with an immortalized cell line that does not reflect the physiology of normal breast epithelial cells; (2) not designed to measure catechol estrogens; and (3) provides no evidence for the "necessary role of catechols" in breast cancer nor genotoxic effects elicited by catechol estrogens in vivo. The second paper, Russo *et al*., Estrogen and its metabolites are carcinogenic agents in human breast epithelial cells, appears to have used estrogen doses much higher than those that might occur in vivo. In addition, this paper reports that MCF-10F cells have estrogen receptors, whereas the first Russo paper concludes that MCF-10F cells do not express estrogen receptors. Without an explanation for this inconsistency, the potential significance and validity of these two studies – the first study in particular – is highly questionable.

derive ADIs."[33] Further, the EC's argument presumes that older data is bad or incorrect data. As we have learned from the experts' responses, this is not the case, but rather it is the quality and quantity of data that is essential.[34]

23. The EC argues that "JECFA did not take the low endogenous levels and thus the high sensitivity of children into account." Again, this conclusion is incorrect. As noted by the experts, JECFA did in fact take sensitive populations into account in its use of safety factors.[35] The EC also opines that use of hormones in oral contraceptives and hormone replacement therapy "demonstrates that estradiol and progesterone are bioavailable through the oral route." It is true that estradiol 17β and progesterone are administered orally for some indications. However, because their bioavailability is so low, very high doses are required to elicit the desired therapeutic effect. For example, therapeutic doses of estradiol 17β for oral administration range from 0.5 - 4.0 milligrams,[36] or 10,000 - 40,000 times higher than the 50 ng. derived from eating beef from cattle treated with estradiol 17β for growth promotion purposes. In addition to high doses, orally administered estradiol 17β and progesterone are also manufactured as micronized formulations (particle size < 10 microns) to further increase bioavailability. Even after micronization, the bioavailability of a 2 mg dose of estradiol 17β is still only about 5%. Lastly, synthetic estrogens used in these treatments have significantly

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[33] JECFA Responses (Question 20), p. 16. *See*, *e.g.*, 1999 CVMP Report, pp. 8-9, citing the 52nd JECFA Report and the 1999 Report of the International Agency for Research on Cancer: "[a]s already demonstrated earlier, the recent studies show that hormonal carcinogens in humans and experimental animals are characterized by (i) tumorigenic action typically in various endocrine responsive organs and/or tissues, and (ii) the need for a prolonged exposure to high concentrations before tumorigenic effects become apparent. The studies are also consistent with the notion of hormone-receptor mediated increase in cell division and proliferation in epithelial cells of the target tissues. This points to a non-genotoxic mode of action, which is in concurrence with (i) the negative results of both earlier and recently performed genotoxicity tests, and (ii) the absence of structural alerts for genotoxicity in the molecule. As cited in the introduction, the recent extensive reviews by IARC and JECFA also confirmed that the tumorigenic action of hormones, in particular 17β-oestradiol, in animals and man are the consequence of the receptor-mediated, cell division stimulating activity of these compounds in somatic target cells, and that the potential genotoxic properties of the compounds would not be expressed in vivo and/or not play a role in the tumorigenic activity."

[34] *See* Dr. Boisseau Responses (Question 34), p. 19 ("the quality and the number of the available data are more important than the dates at which these data have been produced.")

[35] *See* Dr. Boobis Responses (Question 42), p. 39 ("[i]n keeping with its risk assessment principles, the ADI established by JECFA would have been designed to protect all segments of the population, including prepubertal children.") *See* Dr. Boisseau Responses (Question 41), p. 22.

[36] *See* U.S. Department of Health and Human Services Report on Carcinogens, Eleventh Edition, "Estrogens, Steroidal" ("2002 U.S. Report on Carcinogens"). (Exhibit US-26)

higher oral bioavailability compared to the residues of the natural hormone estradiol 17β in meat from treated cattle.[37]

24. Question 9: The EC disagrees with the experts' responses because, according to the EC, "it is today generally accepted that some of these hormones are genotoxic and can cause cancer directly." Although the EC contends that this is the case (and has so concluded in its Opinions), and argues that low doses of the hormones (particularly estradiol 17β) would have a genotoxic effect, it has not supported this conclusion with scientific evidence. The experts' responses, the continuing use of the hormones in cattle for multiple purposes around the world (including in the EC itself), and the intensive study of the hormones by JECFA, Codex and the EC's own CVMP are clear evidence that the genotoxicity of the hormones, particularly at the low levels found in residues in meat from treated cattle, is not "generally accepted."

25. Further, the experts have confirmed that the decision by JECFA to set ADIs for the hormones in 1999 did not mark a change in its conclusion regarding the safety of the natural hormones. In short, as noted in the U.S. Comments, the experts have confirmed that JECFA will only allocate an ADI for a food additive or veterinary drug if the scientific database is complete, unless it can adopt default assumptions that would if anything lead to a more conservative risk assessment than would be the case otherwise.[38] That database was sufficiently complete for the six hormones at issue in this dispute. The EC's failure to support its conclusions with the scientific evidence it relied upon in its Opinions demonstrates that those Opinions are not risk assessments, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement. Nor do the Opinions provide "available pertinent information" for a provisional measure within the meaning of Article 5.7 of the SPS Agreement.

26. Question 10: The EC argues that JECFA has a narrow mandate because it has not examined the likelihood of misuse or abuse of the hormones. As noted by the United States in its comments on the experts' responses, it would be extremely difficult for regulatory or standard-setting bodies to develop international food safety standards based on the assumption of misuse. Any veterinary drug can be misused, and if regulatory authorities base their evaluations against a misuse standard, then there would be virtually no approvals of veterinary medicines. A large number of veterinary drugs marketed around the world have been approved assuming that they would be administered according to good veterinary practices, indicating that this is the norm for such evaluations. It is therefore curious that the EC has not used this standard in its

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[37] For example, the bioavailability of ethinyl estradiol - the synthetic estrogen contained in combination oral contraceptives - is 55%. Fotherby K. Bioavailability of orally administered sex steroids used in oral contraception and hormone replacement therapy. Contraception 1996; 54: 59-69 (cited by Dr. Boobis in his responses to Questions 20 and 40).

[38] Dr. Boobis Responses (Question 9), p. 15; *see* Dr. Boisseau Responses (Question 9), p. 7 ("[t]he Canadian statement stipulating that 'it is recognized that JECFA only allocates an ADI for a food additive or a veterinary drug under review when JECFA considers that its scientific data base is complete and that there is no outstanding scientific issue' is correct."); JECFA Responses (Question 11), p. 10.

evaluation of the six hormones at issue in this dispute, assuming instead extreme misuse scenarios for each hormone.[39]

27. Further, the United States notes that the experts have confirmed that the EC itself has failed to properly examine the likelihood of misuse or abuse of the hormones, as, once it decided to make misuse a mainstay of its analysis, it was obligated to do pursuant to Articles 5.1 and 5.2 of the SPS Agreement.[40] Finally, if misuse of the hormones is the EC's primary concern and not the safety of the hormones at levels actually found in residues in meat from treated cattle, then the EC, by imposing an import ban (whether permanent or temporary) on meat from cattle treated with hormones for growth promotion purposes has breached its obligation to ensure that its sanitary and phytosanitary measures are not more trade-restrictive than required to achieve its appropriate level of sanitary or phytosanitary protection within the meaning of Article 5.6 of the SPS Agreement.

28. Question 11: The EC disagrees with two of the experts' responses (Drs. Boisseau and Boobis) relating to the necessary components of a qualitative risk assessment because, according to the EC, the Appellate Body has determined "that a qualitative risk assessment is equally acceptable under the SPS Agreement and that it does not require the same type of analysis as a quantitative risk assessment." The EC's argument is a *non sequitur*. Nowhere does the Appellate Body determine that, just because a Member need not identify a "certain magnitude or threshold level of risk", that the Member's risk assessment may be devoid of form or scientific rigor. Neither did the Appellate Body grant Members license to assert scientific conclusions in their risk assessments that are unsupported by the scientific evidence.[41] Nor does the Appellate Body stipulate what form a risk assessment must take. Rather, Members must conduct a risk assessment within the meaning of Article 5 and Annex A of the SPS Agreement. The experts

[39] *See* U.S. Comments on the Experts' Responses, fn. 222.

[40] *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.") *See* 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.

[41] This fact has been subsequently confirmed by the compliance panel in the *Japan – Apples* dispute, which found that the scientific conclusions reached by a Member in its risk assessment must actually be supported by the scientific evidence relied on in the risk assessment. *See* Panel Report, Japan – Apples (21.5), para. 8.145 (finding that "[s]ince the scientific evidence relied upon by Japan does not support the conclusions reached by Japan in its 2004 PRA, we conclude that the 2004 PRA is not an assessment, as appropriate to the circumstances, of the risks to plant life or health, within the meaning of Article 5.1 of the SPS Agreement.")

responses are therefore very informative in terms of what does or does not constitute a qualitative risk assessment.[42]

29. The EC also notes that "[i]nterestingly, the US EPA uses no-threshold models for non-genotoxic chemicals, such as dioxins and PCBs, due to a combination of very long half-lives and activity at very low doses." However, the EC's reference to EPA's assessment of dioxin illustrates the stark contrast between the EC's analysis of estradiol 17β and the standard paradigm for risk assessment. EPA's assessment of dioxin did not solely rely on generic arguments of additivity to background as the EC proposes here, but instead reviewed in great depth studies which provided insight into the appropriate approach to extrapolation from low doses to likely exposure levels. The EC's analysis lacks a comparable assessment.

30. Question 12: The EC argues that the responses of Drs. Boisseau and Boobis are incorrect "because of their extremely narrow understanding of the concept of scientific uncertainty." In support of this argument, the EC contends that both Dr. Boisseau and Dr. Boobis have inappropriately relied on the safety factors employed by JECFA in its risk assessments. According to the EC, "there is now almost universal agreement that this approach [*i.e.*, JECFA's use of safety factors] is not scientifically correct." The EC provides no scientific evidence in support of this conclusion. Further, it is unclear how there can be "universal agreement" that JECFA's use of safety factors is "not scientifically correct" when the very two experts asked by the Panel to speak to this issue believe that JECFA's approach is scientifically correct.[43]

31. The EC also cites to the 2002 U.S. Report on Carcinogens as "contradict[ing] the allegations made by the United States . . . in these proceedings, which appears [*sic*] to be supported by Dr. Boobis, that the additional burden of residues coming from eating hormone-treated meat is so small that it would make no difference, compared to the level of endogenous production." Contrary to the EC's claim, in this dispute the U.S. has accepted that concentrations of estradiol 17β may be slightly higher in edible tissues following treatment of cattle with estradiol 17β to promote growth.[44] The United States has simply argued, and demonstrated with evidence, that residue levels of hormones in meat from treated cattle would be

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[42] *See*, *e.g.*, Dr. Boobis Responses (Question 11), p. 16.

[43] For a discussion on sensitive populations, *see* U.S. Comments on the Experts' Responses, Section C.4(c)

[44] *See* U.S. First Written Submission, para. 51 ("Further, concentrations of estradiol 17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, *i.e.*, residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of 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.") (Emphasis added).

within the physiological range of residue levels in meat from untreated cattle.[45] This position is entirely consistent with the statement quoted by the EC from the 2002 Report on Carcinogens.

32. The more complicated question posed to the experts was whether these marginally increased amounts of estradiol 17β are sufficient to elicit effects in the human consumer. As noted in the U.S. Rebuttal Submission, the 2002 Report on Carcinogens indicates that they are not, concluding, "[t]he evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor", in other words, by the much higher concentrations of estrogens necessary to elicit a hormonal effect. Not, as the EC appears to insinuate, by concentrations found in meat products from cattle treated with hormones for growth promotion purposes.[46]

33. As noted by the United States in its Rebuttal Submission, the Report on Carcinogens' conclusion that estrogens are "known to be human carcinogens"[47] is unexceptional when applied to estrogens generally, as it is in the cited Report.[48] As noted in the U.S. First Written Submission, there have been a number of epidemiological tests focused on women and the use of hormone replacement therapies and oral contraception, both of which contain estrogens.[49] The Report on Carcinogens takes these studies into account in its analysis, as well as the conclusions of the 1999 Report of the International Agency for Research on Cancer ("IARC").[50] JECFA

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[45] Indeed, the experts agree with the U.S. statement generally, but disagree as to the number of pregnant cattle actually entering the human food chain. *But see* 2005 Draft Report of the Veterinary Products Committee, Risks Associated with the Use of Hormonal Substances in Food-Producing Animals, § 1.6 ("2005 U.K. Report") (Exhibit US-20) ("In addition, a proportion of cows/heifers entering the food chain are pregnant. Meat from these individuals can also contain higher levels of oestrogen produced by the foeto-placental unit. When the predicted removal of the ban on the inclusion of meat from cattle over 30 months into the food chain occurs, approximately 25% of cull cows entering the food chain are likely to be pregnant (Singleton and Dobson, 1995). Meat from these animals will add significantly to the oestrogen concentrations currently entering the food chain from this source.")

[46] *See* 2002 Report on Carcinogens, p.1. (Emphasis added). Note also that the Report on Carcinogens applies to estrogens generally. ("This listing of steroidal estrogens . . . applies to all chemicals of this steroid class.") (Exhibit US-26). *See* U.S. Rebuttal Submission, paras. 38-40.

[47] Replies to Questions from the Panel after the First Substantive Meeting by European Communities, paras. 98-99.

[48] *See* 2002 Report on Carcinogens, p.1 ("This listing of steroidal estrogens . . . applies to all chemicals of this steroid class.") (Exhibit US-26). Indeed, the 1987 Report of the IARC reached a similar conclusion regarding estrogens generally, but the *Hormones* panel determined that this conclusion had been taken into account by the relevant JECFA safety assessments addressing the relevant risk – that from estradiol 17β residues in meat from cattle treated with the hormone for growth promotion according to good veterinary practices. *See* Panel Report, para. 8.129.

[49] *See* U.S. First Written Submission, paras. 56, 69, 127, 146.

[50] *See* 2002 Report on Carcinogens, p.1. (Exhibit US-26).

took these same studies into account in 1999, noting the "[e]pidemiological studies on women who took estrogens alone or in combination with progesterone and androgens, showed that the risks for cancers at most sites were unaffected; however, the risks for cancers of the endometrium and breast were increased."[51] However, it attributed these effects to the "hormonal effects of estrogens", *i.e.*, to levels of estradiol 17β or other estrogens high enough to have a hormonal effect on the consumer.[52] This is one of the reasons that JECFA determined that levels of estradiol 17β found in meat from cattle treated with the hormone for growth promotion purposes according to good veterinary practices (levels exponentially lower than those causing hormonal effects) are safe.

34. The EC also notes that "neither Dr. Boobis nor Dr. Boisseau mention the fact that the IARC has classified oestradiol-17β in Group 1 as carcinogenic to humans because there is sufficient evidence of carcinogenicity and progesterone and testosterone in Group 2B as possibly carcinogenic to humans." However, the fact that Drs. Boobis and Boisseau have not cited to IARC is not at all surprising in light of the fact that IARC's conclusions do not relate to the levels of any of these hormones found in meat from cattle treated for growth promotion purposes (the subject of this dispute). The EC's CVMP, in concluding that neither estradiol 17β nor progesterone are genotoxic, studied the 1999 IARC Report referred to by the EC in its comments. The CVMP concluded: "the recent extensive reviews by IARC and JECFA also confirmed that the tumorigenic action of hormones, in particular 17β-oestradiol, in animals and man are the consequence of the receptor-mediated, cell division stimulating activity of these compounds in somatic target cells, and that the potential genotoxic properties of the compounds would not be expressed in vivo and/or not play a role in the tumorigenic activity."[53] Therefore, if anything, Drs. Boisseau and Boobis could have cited to IARC in support of the conclusion that any effects of estradiol 17β would result from levels of the hormone causing hormonal effects, rather than the exponentially smaller amounts found in residues in meat from treated cattle.

35. Finally, as noted in paragraphs 13-14 above, despite the EC's statements to the contrary, the conclusions reached by the EC's CVMP on the natural hormones are indeed relevant to this dispute because they relate to the fundamental action of the hormones. At levels lower than those causing a hormonal effect, hormones such as estradiol 17β and progesterone, whether used for growth promotion, or zootechnical and therapeutic purposes are either genotoxic or they are not regardless of whether they are used for growth promotion, zootechnical or therapeutic purposes. The CVMP concluded that they are not.

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[51] 52nd JECFA Report (2000), p. 60. (Exhibit US-5).

[52] 52nd JECFA Report (2000), p. 60. (Exhibit US-5).

[53] 1999 CVMP Report, pp. 8-9 (Exhibit US-5), citing the 52nd JECFA Report and the 1999 Report of the International Agency for Research on Cancer. (Emphasis added). *See also* 2005 U.K. Report, § 1.5.1, ("Overwhelming evidence suggests that sex steroids exert effects that are dose-dependent and that a threshold dose exists, below which, no biological effect will occur.") (Exhibit US-20).

36. Question 13: The EC attempts to discount the advice of Drs. Boisseau (who concludes that "the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans") and Boobis (who concludes that "[t]he EC has not identified the potential for adverse effects on human health of residues of oestradiol found in meat from treated cattle. This is because the analysis undertaken was focused primarily on hazard identification") by noting that JECFA concluded that "the carcinogenicity of oestradiol-17β is most probably a result of its interaction with hormone receptors." The EC's citation to JECFA is puzzling in light of the fact: (1) that JECFA determined that the natural hormones had not been shown to be genotoxic in vivo, and (2) the negative implication of JECFA's conclusion above is that estradiol 17β is not carcinogenic at the exponentially lower levels (non-hormone receptor stimulating levels) found in residues in meat from treated cattle. If the EC is implying that one can hypothesize a risk that estradiol 17β is genotoxic at levels found in meat from treated cattle, such a hypothetical risk alone cannot support its ban on meat and meat products treated with estradiol 17β. And the United States has shown that the scientific evidence does not support this hypothetical risk.

37. Although the EC opines that "carcinogenicity of estrogens is primarily due to oxidative stress/DNA adduct formation caused by the catechol metabolites of estrogens," it has put forward no evidence that catechol metabolites initiate or promote tumors in vivo.[54] In addition, while the EC notes that "it is also necessary to consider estradiol-alpha as residues susceptible to be metabolized in consumer [*sic*] in catechol derivative with the same potency as estradiol to give adducts or to induce oxidative stress," it produces no evidence in support of this conclusion. In cattle, estradiol 17α is the primary metabolite of estradiol 17β. Here, the EC is suggesting that estradiol 17α is present in beef and may be further metabolized in the human consumer to catechol estrogens. This argument is weak for several reasons: (1) Maume *et al*.[55] demonstrated that estradiol 17α concentrations are elevated only in liver and kidney, but not muscle, following administration of a single implant; (2) the EC attempted but was unable to provide evidence estradiol 17α can be converted to catechol estrogens by human intestinal cells[56]; and (3) estradiol 17α does not appear to be carcinogenic[57] and thus does not fit into the EC's theory that estrogens are genotoxic carcinogens (via catechol metabolites).

38. Finally, the EC's support of Dr. Guttenplan's remarks ignores the fact that Dr. Guttenplan notes that "[t]he evidence evaluating the occurrence of adverse effects is weak"[58];

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[54] *See* U.S. discussion of the Bhat and Russo papers in its comments on Question 7 above.

[55] Exhibit EC-78.

[56] Exhibit EC-51C.

[57] Fritsche S. and Steinhart H. Occurrence of hormonally active compounds in food: a review. Eur Food Res Technol 1999; 209:153-179.

[58] Dr. Guttenplan Responses (Question 13), p. 3.

that the EC's Opinions receive a "mixed rating in following Codex guidelines"[59]; that "an adverse effect cannot be ruled out, but it is unlikely if good veterinary practices are followed"[60]; and that, regarding the Syrian hamster model, "[a]s kidney is not a known target of estradiol in humans the extrapolation to humans is uncertain."[61] The EC also cites to additional studies on which it allegedly based its permanent ban on estradiol 17β. Several of these studies were not yet published at the time the EC completed the 1999 or 2002 Opinions on which it allegedly based its ban. Therefore, these studies are not relevant to an analysis of the EC's "risk assessment" or whether its permanent ban on estradiol 17β is based on a risk assessment within the meaning of Article 5.1 of the SPS Agreement. Regardless, as discussed below, none of these studies supports the EC's argument.

39. For example, in Turan *et al*., rats that were exposed continuously to very high doses of estradiol 17β – levels much higher than those derived from beef from cattle treated with estradiol 17β to promote growth – developed mammary tumors. However, treatment of rats with catechol estrogens (the alleged "bad actors" implicated by the EC's genotoxic hypothesis) did not induce tumors. This study confirms the "association of elevated prolonged exposure to endogenous and exogenous estrogen with breast cancer" (a conclusion that is not relevant to the much lower levels of hormones residues found in meat from treated cattle), but it actually provides evidence against the EC's theory that catechol estrogens are the mechanistic basis for this cancer.

40. In Yue *et al*., spontaneous development of mammary tumors was characterized in ERKO/Wnt-1 mice.[62] The authors qualify their results as "preliminary" and point out several pitfalls of interpreting data from ERKO/Wnt-1 mice. In these mice: (1) circulating estradiol 17β levels are 3-5 times higher than normal; (2) the capacity of mammary tissue to inactivate 4-OH estradiol (the alleged "bad actor" in the EC's genotoxic hypothesis) is impaired; and (3) it is possible that low levels of estrogen receptor may be expressed. Therefore, the preliminary results of this study do not provide definitive evidence that mammary tumors can develop in the absence of estrogen receptors. Instead, the results simply indicate that mammary tumors in ERKO/Wnt-1 mice develop in the presence of supraphysiological concentrations of estrogen and abnormally high concentrations of catechol estrogens, and it cannot be ruled out that this tumorigenesis is mediated, at least in part, by estrogen receptors.

41. In Takahashi *et al*., adenocarcinomas were induced in mice exposed subcutaneously to low doses of estradiol 17β in conjunction with intrauterine administration of the chemical carcinogen ENU. As explained in paragraphs 73 and 78 of the U.S. Comments on the Experts' Responses, the subcutaneous (injected into the animal) route of estradiol 17β administration is

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[59] Dr. Guttenplan Responses (Question 14), p. 4.

[60] Dr. Guttenplan Responses (Question 15), p. 4.

[61] Dr. Guttenplan Responses (Question 14), p. 3.

[62] ERKO/Wnt-1 mice are genetically engineered to lack expression of estrogen receptor α.

not relevant to oral ingestion of estradiol in beef (how beef is actually consumed) because it bypasses the extensive first-pass metabolism in the intestine and liver which accompany oral ingestion or consumption of beef. Therefore, the relevance of the Takahashi study to potential effects of estradiol 17β in beef is questionable.

42. The EC also notes that "it is hypothesized that the number of potentially carcinogenic tissue cells determines the risk of getting the cancer," but at the present time this hypothesis is purely speculative, and has not been supported by experimental evidence. As noted in a paper provided by the EC by Smalley and Ashworth, "no definitive identification has been made of an adult mammary stem cell."[63]

43. Finally, the Ahlgren *et al*. paper is an epidemiological study of Danish women which concludes that birth weight and growth during childhood are associated with risk of breast cancer. The Ahlgren study did not examine stem cell populations or exposure to estradiol 17β, and is therefore irrelevant to the analysis at hand.

44. Question 14: The EC appears to cite to Dr. Boisseau's response in support of its contention that it has conducted a risk assessment for estradiol 17β. However, the United States has been unable to locate any support for the EC's position in Dr. Boisseau's response. Instead, the United States notes that Dr. Boisseau comments that the EC "only claims" to have conducted a risk assessment. Nowhere does he note his agreement that the EC has actually done so. As for the EC's citation to Dr. Guttenplan, as noted above, Dr. Guttenplan concludes that the EC's Opinions receive a "mixed rating in following Codex guidelines"; that hazard characterization is "limited" due to the animal model involved (Syrian hamster kidney; kidney is not a known target in humans and therefore extrapolation is uncertain); and that "risk characterization is very qualitative at best." The EC attempts to salvage Dr. Guttenplan's view of its "limited" hazard characterization with citations to studies that were apparently neither included in the Opinions nor presented by the EC in the course of these proceedings in support of its measure.

45. The EC notes that it "disagrees" with Dr. Boobis. The EC provides no rationale for why Dr. Boobis' response is not appropriate or based on the scientific evidence, other than that it feels he has not given the EC Opinions a "careful reading." Most likely the EC disagrees with Dr. Boobis because he concludes that "the EC risk assessment of oestradiol does not follow the four steps of the Codex risk assessment paradigm. Even if it were concluded that oestradiol is a genotoxic carcinogen, the four steps should have been followed."

46. Question 15: The EC notes, for Dr. Guttenplan's "benefit" that the Appellate Body has interpreted "potential" to mean "possible." It is not clear that this clarification is necessary, however, as Dr. Guttenplan already assumed that "[i]f potential is taken to mean possible" adverse effects are "unlikely if good veterinary practices are followed." As for Drs. Boobis and Boisseau, the EC attempts to dismiss their responses by noting that their opinions are

[63] Exhibit EC-100.

"conditioned by their understanding that oestradiol-17β is causing cancer only through receptor meditated processes," a position that, according to the EC "is however scientifically no longer tenable in light of more recent evidence cited by the European Communities." The United States notes that the responses of Dr. Boobis and Dr. Boisseau are premised on a review of the very same evidence referred to by the EC. Drs. Boisseau and Boobis determined, upon review of that evidence, that their understanding is that oestradiol-17β causes cancer only through receptor mediated processes and that the EC has failed to present any evidence that would cause them to conclude otherwise. The EC comments that if the Panel "read[s] between the lines" of Dr. Boobis' and Dr. Boisseau's responses, it will note that they "do not seem to deny completely the existence of possible adverse effects." The EC provides no evidence in support of this conjecture.

47. Dr. Cogliano, while noting that the identification of estradiol 17β as a human carcinogen "indicates that there are potential adverse effects on human health"[64] when it is consumed in meat from treated cattle nevertheless also comments that "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans,"[65] a statement which appears to endorse the conclusion that the EC has failed to demonstrate that carcinogenic or genotoxic effects will be caused by estradiol 17β residues in meat from treated cattle.[66]

48. Question 16: As noted above, the EC attempts to dismiss the opinion of Dr. Boisseau by noting that he has relied on the conclusions of JECFA, which the EC views as outdated, and has ignored the "more recent evidence" cited by the EC "showing the direct genotoxic potential of oestradiol 17β, progesterone, zeranol and most probable [*sic*] testosterone." As demonstrated by the United States and confirmed by the experts' responses, the EC has not shown these effects.[67] Therefore, it is perfectly reasonable for Dr. Boisseau to rely on JECFA's conclusions regarding the hormones. Regarding MGA and trenbolone acetate, the EC notes that "the evidence may be inconclusive but there are sufficient indications to treat them as such [genotoxic], despite the serious gaps in our scientific knowledge." However, the experts' responses have confirmed that these hormones are not genotoxic[68] and that there are not "serious gaps" in the scientific

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[64] Responses to Questions from the Panel of Dr. Vincent Cogliano ("Dr. Cogliano Responses") (Question 15), p. 1.

[65] Dr. Cogliano Responses (Question 18), p. 1.

[66] *See* U.S. Comments on Experts' Responses, para. 43.

[67] *See*, *e.g.*, U.S. Comments on the Experts' Responses, paras. 34-45; 83-85. *See also* Dr. Cogliano Responses (Question 18), p. 1 ("it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels in meat residues added to the pre-existing levels occurring in exposed humans.")

[68] *See*, *e.g.*, Dr. Guttenplan Responses (Question 21), p. 6 ("[t]here is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential.").

knowledge relating to MGA and trenbolone acetate.[69] Indeed, results of one of the EC's own "17 Studies" indicate that MGA was devoid of genotoxic activity, and that trenbolone and zeranol are non-genotoxic except at very high, cytotoxic (*i.e.*, high enough to kill the cell) concentrations.[70]

49. The EC refers to Dr. Boobis' response as "legally inappropriate"[71] in an attempt to discard the factual findings made by Dr. Boobis, which appear to be based on a thorough review of the scientific literature: "[t]he carcinogenic effects of oestradiol appear to be the consequence of its endocrine activity"; and "the guidelines on genotoxicity testing require confirmation of an in vitro positive using an appropriate in vivo assay" (citing to guidance drafted by the EC's own CVMP in 2004).

50. The EC attempts to bolster its argument by claiming that Dr. Guttenplan "concludes that the more recent evidence cited by the European Communities does support the finding that the genotoxic action of these hormones is not related only to their hormonal activity." However, the United States does not understand Dr. Guttenplan's response to be as unequivocal as the EC suggests. Rather, without citation to specific scientific evidence,[72] Dr. Guttenplan on the one hand notes that the EC's Opinions "do indicate that a mechanism other than hormonal activity is possible" but that on the other "the United States and Canada cite other reports indicating that genotoxic effects of estrogens are unlikely." This is far from a conclusion that the studies cited by the EC support the conclusions reached by the EC in its Opinions. Further, Dr. Guttenplan notes elsewhere that while "an adverse effect cannot be ruled out, [] it is unlikely if good veterinary practices are followed,"[73] which would appear to demonstrate that he is not, in fact, of the mind that levels of residues in meat from cattle treated with hormones for growth promotion purposes would be carcinogenic.

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[69] *See*, *e.g.*, U.S. Comments on the Experts' Responses, paras. 49-58. The EC also comments that Dr. Boisseau did not take into account "qualitative assessment of risk" in his response. As noted above, as an expert, there is no reason that he should have since this is a legal determination. In addition, the simple fact is that, regardless of whether a Member conducts a qualitative or quantitative assessment, the conclusions reached in that assessment must actually be supported by the underlying scientific evidence. The experts have confirmed that the scientific evidence relied on by the EC does not support the conclusions it has reached on the hormones (*e.g.*, that they are genotoxic at levels found in residues from meat from cattle treated for growth promotion purposes). *See* Panel Report, Japan – Apples (21.5), paras. 8.145-8.146.

[70] *See* Exhibit EC-8.

[71] As noted above, Dr. Boobis' response, as would be appropriate for any experts' response, does not appear to make any legal statements or findings; it is therefore difficult to see how it is "legally inappropriate".

[72] The United States was unable to locate the citation to the study referred to in the EC's Comments in Dr. Guttenplan's actual response to Question 16.

[73] Dr. Guttenplan Responses (Question 15), p. 4.

51. Finally, on a general note, the United States observes that the EC defines its appropriate level of protection for risks from the six hormones as "no risk from residues of these hormones," as evidence for why its situation is different than that contemplated by JECFA. To date, the United States understood the EC's appropriate level of protection to be one of "no additional or additive risk" from residues of hormones used as growth promoters, particularly in light of the fact that the EC defines its level of protection as such in its 1999 Opinion at Section 1.2 ("[t]he prohibition reflects the fact that the EC chose a level of sanitary protection of accepting no or 'zero' additional risk to human health from the residues in meat and meat products of these hormones when used for growth promotion purposes.") As confirmed by the experts in their responses to Panel Question 51, the EC did not address this risk. If the EC now defines its level of protection as "no risk", it should accordingly ban all uses of the hormones (including the currently permitted zootechnical and therapeutic administrations), as well as the consumption of meat, eggs and any other food products naturally containing any of the six hormones.

52. In addition, the EC notes that its appropriate level of protection is a "quantitative term" (as opposed to the allegedly unacceptable "qualitative" level of protection set by JECFA), yet it goes on in great detail in its comments to argue that it was simply required to conduct a qualitative assessment, and that references to quantitative analyses are inappropriate. At best, the EC's position on what sort of assessment it was required to complete is conflicted, particularly if, as it appears to argue in its comments on Question 16, JECFA's assessment was too "qualitative" for the EC's purposes.

53. Question 17: The United States notes that the EC's conclusion that "as Dr. Guttenplan correctly states, the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity," is unexceptional. Neither does the lack of catechols imply that meat from treated cattle is a risk for genotoxicity.[74] Although the experts agree that the presence of these metabolites would be important to consider in assessing the genotoxic potential of estradiol 17β, they also agree that the materials relied on by the EC failed to detect catechol residues in meat. In the absence of scientific evidence for such residues in meat from cattle treated with estradiol 17β for growth promotion purposes, it is impossible for the EC to conclude that catechol estrogens derived from edible bovine tissues are genotoxic and thus have carcinogenic or tumorigenic effects.[75]

54. The EC notes that "more worrying from the human health point of view is the part of estrogens (estradiol, estradiol-alpha or estrone) which will be metabolized in[to] catechol derivatives in target tissues." However, as noted in the U.S. discussion in Question 13 above, the EC has not provided any evidence to indicate that either estradiol 17α or estrone can be converted to catechol estrogens in humans. The EC comments that this concern "is the reason for which it is necessary to perform a complete residue analysis with more powerful detection

[74] *See* Appellate Body Report, para. 186.

[75] *See generally* U.S. Comments on the Experts' Responses, para. 44.

methods." However, upon review of the exhibits put forward by the EC, it appears as though the EC has already done just this. In Exhibit EC-51A, it is concluded that "[a]n almost complete reassessment of estrogen residues in edible tissues of estradiol-17β treated animals has been performed."[76]

55. The EC also notes that "the fact that exposure to catechol metabolites does not cause mammary tumorigenesis does not necessarily negate the possibility that the catechol metabolites formed in mammary tissue play a role in mammary tumorigenesis . . . because administered metabolites may not reach levels in mammary tissue comparable to those achieved by metabolism of estradiol to the catechols within the mammary itself." However, the credibility of this statement relies on the comparison between concentrations of catechol estrogens in the mammary tissue of experimental animals with those actually found in normal human mammary tissue in vivo. To date, results of this critical comparison have not be reported by the EC.

56. The EC "can only explain[]" the responses of Drs. Boisseau and Boobis by impugning their qualifications and by citing to a remark from a scientist at the meeting of the experts in the original *Hormones* proceedings. The EC presents no scientific evidence that discounts the statements of either Dr. Boobis or Dr. Boisseau. Further, its citation to the Appellate Body remarks appears to focus more on the Appellate Body's concern that the expert in the original proceedings made a claim without any apparent scientific underpinning whatsoever. In contrast, the responses of Drs. Boisseau and Boobis are based on an analysis of the scientific materials on the record in these proceedings.[77]

57. Question 18: The EC notes its agreement with the statement of Dr. Cogliano, but apparently only refers to a limited portion of Dr. Cogliano's response. Dr. Cogliano concludes that "the issue, though is whether [] genotoxicity would occur at levels found in meat residues." As to this issue, "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." Therefore, Dr. Cogliano's response appears to directly contradict the EC's assertion that levels of hormone residues found in meat from treated cattle would be genotoxic.

58. As noted by the United States in its Comments on the Experts' Responses, while Dr. Guttenplan notes that there is evidence that estradiol 17β is genotoxic, he does not conclude that it would be genotoxic at levels found in residues in meat from cattle treated for growth promotion purposes. Indeed, his statement that while "an adverse effect cannot be ruled out, [] it

[76] The results of this comprehensive study were not discussed by Dr. De Brabander, the Panel's expert in residue chemistry.

[77] Dr. Boisseau's response cites directly to the EC exhibit relating to catechol metabolites. Further, it is unclear to the United States what relevant laboratory experience the other two experts have in examining catechol metabolites in hormone residues in meat and meat products; yet, the EC does not complain about their qualifications.

is unlikely if good veterinary practices are followed,"[78] appears to indicate that he is not of this opinion.[79]

59. The EC claims that the issue is "not whether the [EC] has established that genotoxicity and cell proliferation would be induced by levels found in meat residues," but rather whether the United States has demonstrated that "this adverse effect would not occur." This is a remarkable claim by the EC, and a weak attempt to shift the burden of proof. When it chose to impose a ban on meat from cattle treated with hormones for growth promotion purposes premised on its conclusion that the residues would be genotoxic, the EC assumed the burden of proving that this is actually the case. It has failed to do so, and the experts have confirmed this fact in their responses. The United States has argued in detail why the EC has failed to support this conclusion with scientific evidence in its various submissions to the Panel.[80] Further, as noted by the Appellate Body, "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[81] Rather the relevant analysis is whether the EC, in support of its ban, has adduced sufficient evidence to demonstrate a risk from meat from cattle treated with estradiol 17β for growth promotion purposes, including that estradiol 17β is genotoxic at levels found in residues in meat from treated cattle.

60. Finally, the EC dismisses the comments of Dr. Boisseau as "beside the point" and Dr. Boobis as "lack[ing] conviction," yet apart from this rhetoric provides no scientific argument to discount their advice to the Panel. Contrary to the EC's assertion, Dr. Boobis has apparently engaged in extensive analysis, including of the alleged EC evidence claiming in vivo proof of genotoxicity, in reaching his conclusion that "the evidence is against any genotoxicity in vivo." Dr. Boisseau concludes, by citing to his response to Panel Question 13, directly "on point" to the Panel's query: "[i]n conclusion, the EC risk assessment did not support that residues of oestradiol 17β, despite the genotoxic potential of this hormone, can initiate and promote tumors in humans."

61. Question 19: The EC notes that it agrees with the "thrust" of Dr. Guttenplan's response, and then appears to pose a question and offer a response which is not in fact included in Dr. Guttenplan's response. The United States analyzes Dr. Guttenplan's response in detail in

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[78] Dr. Guttenplan Responses (Question 15), p. 4.

[79] The EC cites to a 2006 study it alleges supports Dr. Guttenplan's statement, yet that was not cited by Dr. Guttenplan himself. The United States notes that the date for submission of scientific evidence is well-past, and that the EC reached its definitive conclusion (such that it imposed a permanent ban) on this issue in 2003. It is therefore unclear how a 2006 study can justify Opinions drafted and a measure adopted three years prior to its publication.

[80] *See*, *e.g.*, U.S. First Written Submission, paras. 152-153; U.S. Rebuttal Submission, Section II.B(3), pp. 15-18 (titled "The EC's Opinions fail to take into account available scientific evidence relating to genotoxicity and carcinogenicity of estradiol 17β")

[81] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

paragraph 38 of its Comments on the Experts' Responses. The EC also notes that "although DNA repair can occur, it presumably is occurring at all doses and the fraction of DNA damage repaired probably does not change at physiological levels, because the repair enzymes are unlikely to be saturated." This statement, which the EC attributes to Dr. Guttenplan, appears to further highlight the fact that the EC should have (but failed to) taken DNA repair mechanisms into account in its Opinions. Further, since, as confirmed by the EC, the repair enzymes are not saturated under physiological conditions, then it stands to reason that these enzymes have the capacity for increased activity when exposed to xenobiotics or elevated concentrations of endogenous genotoxic substances.[82] Therefore, increased activity of DNA repair enzymes is a protective mechanism against DNA damage. Of course, the capacity for increased enzyme activity is finite and can be overwhelmed (*i.e.*, saturated) in the face of very high exposure to genotoxic compounds, but there is no evidence that this will occur in response to the very low amounts of estradiol 17β in meat from treated cattle.

62. The EC notes that "[a]fter all, whether cancer will occur as a result of genotoxicity or hormonal action is from the regulatory point of view less critical, as the end result is the same: human cancer." This statement seems contradictory to the EC's arguments to date. The EC has devoted considerable time, effort and resources in its attempt to demonstrate that estradiol 17β is genotoxic in vitro, but has failed to provide convincing evidence that genotoxicity is the basis for estrogen-induced carcinogenicity in vivo.

63. The United States has not been able to locate the statement ascribed to Dr. Boisseau by the EC in Dr. Boisseau's response, but notes Dr. Boisseau's conclusion that "[t]he scientific evidence referred to by the [EC] does not demonstrate that this statement can also apply in the case of oestradiol-17β, progesterone and testosterone as these three natural hormones are produced by both humans and food producing animals." As such, Dr. Boisseau's response appears to address the EC's concern that he somehow was not aware of, or ignored the studies cited in the EC's Opinions. The EC cites to the Hilakivi-Clarke paper discussed in detail at paragraph 74 of the U.S. Comments on the Experts' Responses.

64. The EC also notes that Dr. Boisseau's statement "cannot be accepted scientifically" because "[i]n the EC's view, it is beyond doubt that there is a link between 17β-oestradiol exposure during development . . . and the risk of breast cancer later in life." However, the "EC's view" of the scientific evidence and what the scientific evidence actually demonstrates are two distinct concepts. The EC has failed to demonstrate that the scientific evidence actually supports its view.[83]

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[82] *See* Brusick D. Principles and Methods of Toxicology, 4th Ed., 2001, p. 825.

[83] *See* the Responses of Drs. Boisseau, Boobis, Cogliano and Guttenplan to Panel Question 26 ("Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the

65. The EC does not provide any evidence or argument to discount Dr. Boobis' advice ("[t]here is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this. Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance.")

66. Question 20: The EC notes that Dr. Boobis' response "is based on his more erroneous underlying assumption that oestradiol-17β is not genotoxic" and continues by noting that if Dr. Boobis' "assumptions are false, as the scientific evidence clearly demonstrates, the Dr. Boobis' statement – which is already a qualified one – would make no sense." The United States has noted at several points above that Dr. Boobis' conclusions are indeed based on the scientific evidence, and that it is the EC who has failed to adduce the necessary evidence to support the conclusions it has proposed regarding estradiol 17β. Further, Dr. Boobis' conclusions ("I do not believe that JECFA's conclusion that oestradiol has 'genotoxic potential' affected its recommendations on this hormone"; "JECFA's conclusion on genotoxicity was based on positive results in certain in vitro tests, but the evidence was against a mutagenic response in vivo") are supported by the responses of JECFA itself.[84] The EC also notes that the responses of Drs. Boisseau and Boobis should be discounted because "they have not done any direct experiments on these hormones in their professional life and so lack specific expertise." The United States has commented on this issue at several points above. In this particular instance, judging from their *curriculum vitae*, it would appear that Drs. Boisseau and Boobis have more relevant experience in terms of JECFA and Codex decision making than any of the other experts.

67. The EC faults Drs. Boobis and Boisseau for "consider[ing] the assessments of JECFA as the Bible, although they know that the 1988 and 1999 JECFA assessments are outdated by today's evidence and scientific standards." Nowhere in the responses of either expert was the United States able to locate a statement along these lines. Rather, the responses of the two experts indicate that they do not believe the JECFA assessments to be "outdated."

68. The EC also notes that, since the original *Hormones* dispute, the EC "has been consistently arguing [that] the genotoxicity of oestradiol-17β is no longer seriously disputed and has now for the first time been accepted and written in the 1999 JECFA report." On the one hand, the fact that the EC has been arguing a point does not mean that the point is actually supported by scientific evidence. In fact the EC made this argument in the original dispute and is here simply trying to overturn established WTO findings. Indeed, the experts have confirmed that, insofar as the issue of genotoxicity relates to hormone residues in meat from cattle treated

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consumption of meat from animals treated with the hormones at issue?") The experts unanimously confirm that the EC has not demonstrated a link between consumption of hormones residues in meat and breast cancer.

[84] *See* U.S. Comments on the Experts' Responses, para. 41.

for growth promotion purposes, the evidence does not demonstrate a genotoxic effect.[85] On the other hand, the experts have confirmed that JECFA's statement of "genotoxic potential" did not affect its ultimate conclusion that the use of the hormones as growth promoters in cattle is safe.[86]

69. In addition, the EC poses several questions to Dr. Boobis regarding whether he can "provide the necessary assurance" to EC authorities that residues in meat "will not increase the risk of cancer." The United States believes that the EC's rhetoric is entirely inappropriate for this exercise, in which the experts were requested to provide responses on specific scientific issues presented by the Panel. The insinuation that Dr. Boobis is responsible for providing an assurance to the EC on these matters appears to be nothing more than a thinly-veiled attempt to coerce Dr. Boobis into changing his clear scientific opinions and honest review of the materials put forward by the EC in support of its ban. Further, as noted by the Appellate Body, "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[87] Rather the relevant analysis is whether the EC, in support of its ban, has adduced sufficient evidence to demonstrate a risk from meat from cattle treated with estradiol 17β for growth promotion purposes. The United States could just as easily ask the EC if it can provide the necessary assurance to the United States that EC exports of alcoholic beverages will not increase the risk to human health, or that EC exports of agricultural commodities will not increase the risk of exotic pests? No one can provide assurance that a risk could never be identified in the future, nor does the SPS Agreement call for such an assurance. Rather the question is what does the current scientific evidence and principles support.

70. Further, the EC quotes the Appellate Body's statement that, while in most cases responsible governments base measures on "mainstream" evidence, "[i]n 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." Be this as it may, it is clear that the Appellate Body did not exempt Members from providing a scientific basis and scientific evidence in support of that "divergent opinion",[88] and as argued by the United States and confirmed by the experts in their responses, the EC has failed to adduce the necessary evidence to support its "divergent opinion."

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[85] *See* U.S. Comments on the Experts Responses, Sections C.2 and C.3(b).

[86] *See* U.S. Comments on the Experts Responses, para. 41.

[87] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

[88] *See* Panel report, Japan – Apples (21.5), paras. 8.145-8.146.

71. Finally, the EC cites again to the 2002 Report on Carcinogens. As noted in the U.S. comments on the EC's comments on Question 12 above, this document simply does not stand for the conclusions drawn from it by the EC.[89]

72. Question 21: The EC notes that it is "puzzled" by the responses of Drs. Boobis and Boisseau. Although the EC claims that JECFA "was more prudent" in its decisions than both of these experts, the United States fails to see any significant inconsistency between JECFA's conclusions on the hormones and those of Drs. Boobis and Boisseau. The EC claims that its Opinions "provide enough evidence to demonstrate that genotoxicity and other adverse effects from the hormones are possible," but the experts (including not just Drs. Boobis and Boisseau, but Dr. Cogliano) disagree, particularly if the EC is referring to levels of the hormones that would be found in residues in meat from cattle treated for growth promotion purposes.

73. The EC attempts to bolster its argument by noting that "[a]s Dr. Guttenplan states, their [the five hormones'] genotoxic potential may be weak but cannot be excluded." However, this statement fails to take into account the other conclusions reached by Dr. Guttenplan: "[t]here is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential," and:

> [t]estosterone and progesterone are negative in genotoxic assays. Zeranol can induce transformation of breast epithelial cells in culture with efficiency similar to that of estradiol, but the mechanism is not known, and it is negative or marginally active in other assays. Trenbolone is either negative or marginally active in in vitro genotoxic assays. MGA is negative in genotoxicity assays. Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice. My reply for the hormones would not have been different in September 2003 (SCVPH 2002 Opinion).

It is clear from the actual text of Dr. Guttenplan's response that he does not endorse the EC's argument that the five hormones are genotoxic.

74. The EC notes that it has provisionally banned the five hormones "taking into account the numerous and serious gaps in our scientific knowledge, which have been clearly identified in the SCVPH assessments." However, as noted in Section C.3(c) of the U.S. Comments on the Experts' Responses, the experts have not identified "numerous and serious" gaps in the scientific knowledge relating to the five hormones.[90]

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[89] *See* U.S. Comments on the Experts' Responses, para. 41 and fn. 97 for discussion of the responses of Drs. Cogliano and Guttenplan. *See also* U.S. Rebuttal Submission, paras. 38-40.

[90] *See generally* Responses of the Experts to Panel Question 61 and 62. *See* U.S. Comments on the Experts' Responses, Section C.3(c) for a discussion of Dr. Guttenplan's response to Question 62.

75. Question 22: The EC appears to have omitted a significant portion of Dr. Boobis' response, in which he concludes, "[t]he DNA repair processes [] are amongst the most efficient (Arai et al., 2006; Russo et al., 2004) and even if such modification did occur, it is anticipated that no heritable change would result, because of DNA repair (Arai et al., 2006). This would be true even at the levels of exposure that could arise should GVP not be followed." The EC then argues that, if everything Dr. Boobis assumed were in fact false, then he would have come to a different conclusion and he "should accept that DNA repair mechanisms are not sufficient to eliminate DNA damage." The EC's argument is nonsensical, as the evidence underlying Dr. Boobis' response is not false, and he does not in fact endorse this conclusion.

76. The EC attempts to cast doubt on the response of Dr. Guttenplan by noting that both he and Dr. Boobis "appear to miss an important point" but fails to present any evidence that discounts Dr. Guttenplan's conclusions on DNA repair mechanisms: "[t]here is no reason to assume that DNA repair processes involved in DNA damage produced by estrogen metabolites are any more or less effective than those involved in repair of other carcinogens"; and "[t]he scientific material referred to by the [EC] for the most part doesn't address DNA repair."[91] The United States provides additional discussion on DNA mechanisms in its comments on Question 19 above.

77. Question 23: The EC agrees with the statements of Drs. Cogliano and Guttenplan that a sufficiently long latency period for cancer should be taken into account in the conduct of a risk assessment. The United States notes that Dr. Boobis also agrees on this point, which is unexceptional in the context of this dispute since the six hormones at issue have been used for growth promotion purposes in meat for a sufficiently long time (decades) to address this concern. Dr. Boisseau: "the hormones in dispute have already been used as growth promoters over a sufficient number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters." Dr. Boobis: "[t]he observational studies of humans (e.g. on HRT or oral contraceptives) and the experimental studies in animals covered a sufficiently long period to encompass the latency period for any carcinogenic effects of the hormones." Dr. Guttenplan: "[w]ith respect to hormones in meat, it appears they have now been consumed for a sufficient number of years to observe strong or moderate increases in risk."

78. Question 24: The EC avers that the experts' responses on confounding factors "also undermine indirectly the position of the U.S." without providing any argument or explanation for why this is so. The EC cites again to a study regarding the frequency of breast cancer (cited in its 1999 Opinion) and purports to draw a link between the use of hormones for growth promotion purposes and the incidence of cancer. The experts have dismissed this link in their responses to Panel Question 26 (Boisseau: (citing to his response to Question 23) "the hormones in dispute

[91] *See* U.S. Comments on the Experts' Responses, para. 31 for further discussion of Dr. Guttenplan's response on DNA repair mechanisms.

have already been used as growth promoters over a sufficient number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters; Boobis: "[t]here is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans; Cogliano: "[t]he data [relating to the difference in breast cancer rates] are not sufficiently specific to establish a link between these observations"; Guttenplan: "[t]he epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters. The references to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities are not very convincing as there is considerable variation in rates in different geographical locations. Also, the differences in rates of breast and prostate cancer observed in the United States as compared to the European Communities are relatively small.")

79. Question 25: The EC again attempts to dismiss the response of Dr. Boobis by questioning his qualifications as an expert. This has been addressed at several points above. The EC also alleges that JECFA's views are "based on data from the 1970s – 1980s" and that the EC has now provided "more recent evidence." The statement regarding the dates of materials examined by JECFA is simply false. For example, at its 52nd Meeting in 1999, JECFA evaluated several pieces of recent scientific evidence. Indeed, the EC recognizes this fact in its Opinions.[92] Further, the "more recent evidence" put forward by the EC does not support the conclusions for which the EC cites to it in its Opinions.

80. The EC argues that Dr. Boobis has taken an "absolutist" approach, and attacks his response by alleging that Dr. Boobis requires "positive proof of harm," and that rather evidence should be provided of a lack of possible harm. The Appellate Body noted the following regarding the alleged need to provide evidence of a lack of harm: " [i]n one part of its Reports, the Panel opposes a requirement of an 'identifiable risk' to the 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."[93] As is clear from its comments on Dr. Boobis' response, rather than providing actual scientific evidence of a risk to consumers from the consumption of residues in meat from cattle treated for growth promotion purposes and basing a measure on the risk assessment drawn from that evidence, the EC would instead opt to focus on the very theoretical uncertainties described by the Appellate Body in support of its ban on meat and meat products from cattle treated with estradiol 17β. All of this is a distraction from Dr. Boobis' response, which categorically notes that the three recent studies referred to by

[92] *See*, *e.g.*, 1999 Opinion, p. 77 ("However, in the 1999 report of JECFA, more recent work on biotransformation mediated genotoxicity was cited.")

[93] Appellate Body Report, para. 167.

the EC "do[] not confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones."

81. The EC agrees with the comments of Dr. Cogliano, which is surprising since Dr. Cogliano's comment on the Norat study is that it indicates a risk to human health from meat generally[94], and his comment on the other two studies is qualified by the fact that "the exposure levels found in these studies are higher than those found in meat residues." The EC cites very selectively to Dr. Guttenplan's response, which is understandable since he concludes the following regarding the first EC study (Liu and Lin): "the results were obtained in cultured cells and the relevance to human exposure to hormone-treated [meat] cannot be extrapolated from this study because of a myriad of uncertainties in such extrapolation." He concludes the following regarding the second and third studies: "[t]he other two studies do not confirm a risk from hormone-treated meat." The results of the Liu and Lin paper are questionable due to lack of a dose response. The authors claim to have data that meat and serum from zeranol-implanted cattle are mitogenic and estrogenic, but their reports are all in abstract form (not publicly available). The U.S. FDA has approached the authors for more information, but they have not responded to repeated requests.

82. Question 26: The United States has addressed the issue of the experts' responses on epidemiological studies at several points above. The EC's comments ignore the conclusions reached by each of the experts. Boisseau: (citing to his response to Question 23) "the hormones in dispute have already been used as growth promoters over a sufficient number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters." Boobis: "[t]here is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans." Cogliano: "[t]he data [relating to the difference in breast cancer rates] are not sufficiently specific to establish a link between these observations." Guttenplan: "[t]he epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters. The references to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities are not very convincing as there is considerable variation in rates in different geographical locations. Also, the differences in rates of breast and prostate cancer observed in the United States as compared to the European Communities are relatively small."

83. The EC notes that it "advanced this [epidemiological] argument to demonstrate that the scientific uncertainty is growing concerning the harmless nature of the residues of these hormones." (Emphasis in original). However, as evidenced by the experts' responses, the EC has demonstrated no such uncertainty. Further, as noted by the Appellate Body, "theoretical

[94] *See* U.S. Comments on the Experts' Responses, para. 63.

uncertainty is not the kind of risk which, under Article 5.1, is to be assessed,"[95] and "the existence of unknown and uncertain elements does not justify a departure from the requirements of Articles 5.1, 5.2 and 5.3, read together with paragraph 4 of Annex A, for a risk assessment."[96]

84. Finally, while the EC downplays the role of epidemiological studies in its decision making in its 1999 Opinion, noting that it "cited this epidemiological evidence in the 1999 SCVPH [Opinion] not as an affirmative [*sic*] or adequate proof but just as an indication and possible explanation", it was not so circumspect in the actual 1999 Opinions, and in fact linked several of that document's "Major Conclusions" directly to the epidemiological data: "[e]pidemiological studies have demonstrated strong relationships between the levels of endogenous oestrogen and risk of breast cancer (Toniolo, et al., 1995; Berrino, et al., 1996; Bernstein, et al., 1990 a and b; Shimizu, et al., 1990; Pike, et al., 1992)" (1999 Opinion, p. 42); "[a]s concerns excess intake of hormone residues and their metabolites, and in view of the intrinsic properties of hormones and epidemiological findings, a risk to the consumer has been identified with different levels of conclusive evidence for the 6 hormones in question" (1999 Opinion, "Major Conclusions", p. 73); "[i]n view of the intrinsic properties of the hormones and in consideration of epidemiological findings, no threshold levels can be defined for any of the 6 substances" (1999 Opinion, "Major Conclusions", p. 73). (Emphasis added).

85. As demonstrated above, the experts disagree that this epidemiological evidence supports the conclusions for which it is cited by the EC. Further, as noted by the compliance panel in *Japan – Apples (21.5)*, the scientific materials underpinning a risk assessment must actually support the conclusions reached in that assessment.[97] Materials that do not provide "affirmative [*sic*] or adequate proof" cannot be said to support the conclusions reached by the EC in its 1999 Opinion. The EC has therefore failed to conduct a risk assessment, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement for estradiol 17β.

86. Question 27: It is unclear why the EC thinks that the results of Stephany are "completely different" than those used to support approval of estradiol 17β as reported in the 1999 JECFA Report. The concentration of estradiol 17β reported by Stephany in "M/LQ domestic US beef", 0.03 ppb (equal to 30 nanograms/kilogram), is well within the range of estradiol 17β concentrations in muscle reported by JECFA which range from 0.5 - 117 nanograms/kilogram. Although the average concentrations are correctly quoted from Table 5 of Stephany's paper, Stephany uses the median values to make the statement that "it is estimated that the median

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[95] Appellate Body Report, para. 186.

[96] Appellate Body Report, *Australia – Measure Affecting Importation of Salmon*, adopted on 6 November 1998, WT/DS18/AB/R ("Australia – Salmon"), para. 130.

[97] *See* Panel Report, Japan – Apples (21.5), paras. 8.145-8.146 (finding that "[s]ince the scientific evidence relied upon by Japan does not support the conclusions reached by Japan in its 2004 PRA, we conclude that the 2004 PRA is not an assessment, as appropriate to the circumstances, of the risks to plant life or health, within the meaning of Article 5.1 of the SPS Agreement.")

dietary intake of 17β-estradiol via a 250 gram steak of 'Hormone Free Cattle' is less than 2.5 nanogram and via 250 gram 'beef' of 'Hormone Treated Cattle' is 5 nanogram", *i.e.*, a 2-fold difference. It is assumed that Stephany used the median values for this comparison because these values, not average values, are most appropriate to use when assessing lifetime dietary exposure to a residue or contaminant in food (*see* 1999 JECFA report, p. 83). Thus, the 7.5-fold difference in estradiol-17β concentrations in beef between treated and untreated cattle cited by the EC may be considered an exaggeration.

87. Further, the EC provides no support from the experts' responses for its conclusion that "the difference in the residues is not only structural/chemical but also qualitative and quantitative," and in fact makes no reference whatsoever to the response of the relevant scientific expert, Dr. Boisseau.

88. Question 28: The EC comments that Dr. Boisseau's response ("[i]n the case of . . . residues of the natural hormones, which consist of parent substances, there is no difference between hormones naturally present in food producing animals, meat or human beings") is "partially incomplete and partially false." The EC refers again to catechol metabolites of estradiol 17β, noting specifically that estradiol 17α, alleged by the EC to be the main residue in cattle liver, "may react with nucleophilic compounds and induce some disruptions." The EC's suggestion that estradiol 17α is present in beef and may be further metabolized in the human consumer to catechol estrogens is weak for several reasons: (1) Maume *et al*.[98] demonstrated that estradiol 17α concentrations are elevated only in liver and kidney, but not muscle, following administration of a single implant (muscle is the tissue most often consumed); (2) the EC attempted but was unable to provide evidence estradiol 17α can be converted to catechol estrogens by human intestinal cells[99]; and (3) estradiol 17α does not appear to be carcinogenic[100] and thus does not fit into the EC's theory that estrogens are genotoxic carcinogens (via catechol metabolites). In addition, estradiol 17α is a relatively weak estrogen, with only 10% of the in vivo potency of estradiol 17β and concentrations of estradiol 17α are undetectable in muscle, which is consumed in much greater quantities than liver.

89. The EC notes that Dr. De Brabander's statement is "very informative", but the United States notes that Dr. De Brabander's response fails to cite any scientific evidence in support of its conclusions, which appear to miss the point of the Panel's query. The Panel's question speaks to differences in the fundamental composition of the hormones in their basic form (*i.e.*, is estradiol 17β in the human body the same as estradiol 17β residues in meat). Dr. De Brabander's response provides speculation as to how the body breaks down or metabolizes the

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[98] Exhibit EC-78.

[99] Exhibit EC-51C.

[100] Fritsche S. and Steinhart H. Occurrence of hormonally active compounds in food: a review. Eur Food Res Technol 1999; 209:153-179.

hormone, making a vague reference to body builders. The process of metabolization of the hormones has been discussed in detail above.[101] Further, the EC's endorsement of Dr. De Brabander's "finding that the residues of the endogenously produced natural hormones in cattle are in the 17α form (inactive) while the use of the natural hormones for growth promotion purposes may lead to residues in the β form (active form)," suggests that tissue residues of estradiol 17β in cattle treated with estradiol 17β for growth promotion purposes are qualitatively different from residues in untreated cattle. This is incorrect, as demonstrated by the results of the EC's own "17 Studies",[102] which showed that edible tissues from untreated cattle and cattle treated with a growth-promoting implant contain both estradiol 17β (muscle, liver, kidney) and estradiol 17α (liver and kidney only (no muscle)).

90. Question 29: The EC disagrees with Dr. Boisseau, who determined upon evaluation of the SCVPH Opinions that the EC failed to evaluate actual residue levels of the synthetic, provisionally-banned hormones. However, Dr. Boisseau's response (which cites to the EC's 1999 Opinion) is indeed supported by the text of that Opinion (in the "Major Conclusions" section): "[i]n view of the intrinsic properties of the hormones and in consideration of epidemiological findings, no threshold levels can be defined for any of the 6 substances." As confirmed by the responses of the experts, this conclusion is without scientific support. Therefore, it is clear that the EC has not based its provisional ban on these hormones on "available pertinent information" (which indicates that thresholds can indeed be set) within the meaning of Article 5.7 of the SPS Agreement.

91. Dr. De Brabander does not appear to offer a specific opinion as to whether the EC's Opinions indeed evaluate these residue levels, though he notes that "the assessment of risk as evaluated by the SCVPH is in terms of actual residue levels is less complex than in the case of the natural hormones"[103] which would appear to indicate that the EC's evaluation was less than robust. Nevertheless, the EC notes that Dr. De Brabander "confirms the EC argument that the data used by JECFA are not only too old but have also been obtained with methods that are no longer reliable today."

92. The United States notes that the residue data used to support approval of the growth promoting hormones are reviewed in the 52nd JECFA Report. Included in this Report is a very detailed description of the method (developed in 1979 and revised in 1982 and 1983) used to generate these residue data and four pages of data which describe the method's performance (percent recovery, range of assay detection, intra- and inter-assay variability, assay precision). Therefore, all of the information required to evaluate the methods used to generate the residue

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[101] *See*, *e.g.*, Questions 13 and 17 above.

[102] Exhibit EC-78.

[103] Responses to Questions from the Panel of Dr. Hubert De Brabander ("Dr. De Brabander Responses") (Question 29), p. 3.

data used by JECFA in its determinations have been publicly available since 1999. Despite this fact, neither the EC nor the scientific expert on residues (Dr. De Brabander) has provided a scientific review or analysis of these data explaining why or how the methods are "no longer reliable today", nor do they provide any reasons for why the methods were not adequate to derive MRLs. Instead, they opt to dismiss them as unreliable simply because they are "old." As explained in the U.S. Comments on the Experts' Responses at footnote 193, JECFA has specific and extensive requirements for residue data. Therefore, these "old" data were critically reviewed by JECFA experts in 1999 and deemed to be of sufficient quality to assess the human food safety of hormone residues in beef.

93. Question 30: The EC attempts to dismiss the response of Dr. Boisseau for the same unfounded reason cited in its comments on Question 29 above. The EC opines that Dr. Boobis is "clearly wrong" because, according to the EC, it has completed a "detailed exposure assessment" for the three natural hormones. Yet, both Drs. Boobis and Boisseau, upon review of the EC's materials, disagree. Dr. Boobis notes, as has been argued by the United States, that rather than evaluating actual residue levels of the natural hormones, the EC instead concocts several misuse scenarios in its attempt to demonstrate a risk to consumers.[104]

94. The EC claims to have "not only considered the ADIs and MRLs set by JECFA but went even further and examined the acceptable levels and tolerances recommended by the USA." The United States notes that the Panel's inquiry was whether the SCVPH considered or examined actual residue levels (*i.e.*, those reported by Stephany). These are not the same as and are, in general, much lower than ADIs, acceptable levels and tolerances. Therefore, the EC's calculations in its Opinions greatly overestimate the actual consumption of hormone residues.[105]

95. Question 31: The EC provides no scientific evidence to dispute Dr. Boisseau's comments or the U.S. statement in its first written submission regarding hormone residue levels in treated and untreated meat. Rather, it cites again to the 2002 Report on Carcinogens in an attempt to bolster its arguments. The United States discusses its argument on residue levels as well as the relevance of the 2002 Report on Carcinogens in detail in its comments on Question 12 above. The EC also notes that levels of residues in meat "are not unimportant, as the earlier comments of the [EC] on the absence of a threshold have demonstrated." The EC has not demonstrated the absence of a threshold. The experts' responses confirm this fact.[106]

96. The EC states that Dr. De Brabander discussed one of its studies indicating "that the consumption of meat from the regular hormone treated meat market in the U.S. contains 7.5

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[104] *See* Dr. Boobis Responses (Question 30), p. 33.

[105] *See* U.S. Comments on the Experts' Responses, paras. 92-96 for a discussion of Dr. De Brabander's response.

[106] *See*, *e.g.*, Experts' Responses to Panel Question 15.

times more estrogens than in meat from untreated cattle." However, the United States was unable to locate this conclusion in Dr. De Brabander's response. The United States discusses the EC's argument regarding the "7.5 times" higher levels of estradiol 17β in detail at paragraph 86 above. Similarly, the United States could not locate the following conclusion ascribed to Dr. De Brabander in his response to Question 31: "the [EC] considers that the reply of Dr. De Brabander rightly points out the increased risk which repetitive exposure to such higher residues can present to the most sensitive parts of the population."[107]

97. Question 32: The EC avers that Dr. Boisseau's response is "scientifically unsound", yet provides no scientific evidence or discussion for why this is so.[108] The EC also notes that "there is an urgent need to apply the latest analytical methods to determine the nature and level of the residues from these hormones and all their metabolites, which is perplexing since a review of the exhibits put forward by the EC indicates that the EC believes it has already accomplished this. In the EC-sponsored study described in Exhibit EC-51A, it is concluded that "[a]n almost complete reassessment of estrogen residues in edible tissues of estradiol-17β treated animals has been performed."

98. Question 33: The EC concludes that the responses of Dr. Boisseau and Dr. Boobis are "conflicting", yet provides no scientific evidence or discussion for why and where this is so. The EC cites to Dr. De Brabander of the proposition that residue data examined by JECFA should "no longer be considered to be credible or reliable", yet it provides no scientific evidence in support of the conclusion that the earlier residue data is no longer adequate.

99. The EC appears to take Dr. Boobis' comment relating to the three natural hormones (the subject of the Panel's question) (Dr. Boobis: "the view was that it was unnecessary to conduct a detailed evaluation of the toxicology of substances produced endogenously [*i.e.*, naturally]" in 1988) and attempt to use it to support the following conclusion: "Dr. Boobis admits that the 1988 evaluation was made by JECFA even without toxicological monographs, which means, *inter alia*, that for the two synthetic hormones - trenbolone acetate and zeranol - which have not been evaluated since 1988, JECFA's conclusions are no longer reliable." However, Dr. Boobis' comments on the natural hormones are unrelated to the synthetic hormones (and therefore do not support the EC's conclusion), which were not even the subject of the Panel's question.

100. The EC quotes Dr. Boobis' comment that, over time "it became clear that exposure to the natural hormones, albeit at levels appreciabl[y] higher [than] that found in meat from treated cattle, could have adverse effects on human health," as support for its arguments. However, Dr. Boobis' conclusion, which notes that recent epidemiological evidence demonstrated that

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[107] *See* U.S. Comments on the Experts' Responses, paras. 92-96 for a discussion of Dr. De Brabander's response.

[108] *See* U.S. Comments on the Experts' Responses, para. 93 for a discussion of Dr. De Brabander's response.

hormones caused effects "at levels appreciably higher than that found in meat from treated cattle" contradicts the EC's argument that the exponentially lower levels of hormone residues in meat from treated cattle pose a risk, and instead supports arguments put forward by the United States in its submissions to the Panel.[109]

101. The EC agrees with Dr. De Brabander that data relating to the three natural hormones should "no longer be considered to be credible and reliable." Yet, as noted in Question 29 above, there is no scientific analysis provided by either the EC or Dr. De Brabander for why this is so.

102. Question 34: The EC comments that Dr. Boisseau "agree[s] that the data used by JECFA are old," and notes that his argument "to minimize the importance of their old nature" is "not scientifically sound." As evidence of this fact, the EC states: "concerning estradiol-alpha, which is the main metabolite found in target tissue (liver) of treated cattle and which we know that it will be metabolized in[to] catechol derivatives, no specific evaluation of the genotoxic mechanism has been performed by JECFA." However, as discussed in detail in Questions 13 and 17 above, the EC has not provided any evidence to indicate that estradiol 17α can be converted to catechol estrogens in humans. The EC has failed to cast doubt on JECFA's determination that estradiol 17β is not genotoxic at levels found in residues in meat from cattle treated for growth promotion purposes.

103. As was the case when the EC was faced with a response from Dr. Boobis to which it had no response (Question 20), the EC asks "[c]an Dr. Boisseau provide an assurance to the [EC] that JECFA's conclusions would have not been different if more recent and accurate data were available to it?" The United States rejects the implicit assumption in the EC's question that the data relied on by JECFA are inaccurate or that there is more recent or accurate data available. Furthermore, as noted above in the comments in relation to Question 20, the United States believes that the EC's rhetoric is entirely inappropriate for this exercise, nor could the EC provide any such assurance with respect to its own exports. As the United States has demonstrated time and again, and the experts have confirmed, the EC has not adduced any scientific evidence which would call into question JECFA's determinations on the safety of the hormones. Further, as noted by the Appellate Body, "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[110] Rather the relevant analysis is whether the EC, in support of its ban, has adduced sufficient evidence to demonstrate a risk from meat from cattle treated with estradiol 17β for growth promotion purposes or that the available pertinent information supports a provisional ban on the other five hormones.

104. Question 35: The EC comments that Dr. Boisseau agrees that the data evaluated by JECFA on MGA "date[s] from the 1960s and 1970s". The EC refers to its comments on

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[109] *See*, *e.g.*, U.S. Rebuttal Submission, paras. 38-39.

[110] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

Question 34 to allegedly support its conclusion that Dr. Boisseau is incorrect in asserting that, just because the evidence is older does not mean that it is bad or inadequate. However, the quality and quantity of the evidence point to the opposite conclusion. As further evidence of this fact, the EC has failed to put forward scientific evidence that would cast doubt on JECFA's conclusions on MGA. This is confirmed by the experts' responses to Questions 61 (is there sufficient scientific evidence to conduct a risk assessment for MGA)[111] and 62 (are there any gaps in the scientific information relating to MGA).

105. The EC argues that "the 'low-dose' issue was not recognized in peer-reviewed literature before the mid 90s. Therefore, all the research into possible low-does effects has not been considered in the 2000 JECFA Report." It is unclear, however, exactly what "low-dose effects" the EC is referring to here.

106. The EC also concludes that Dr. Boisseau's response is incorrect "[i]n the light of the new evidence provided by the European Communities in its risk assessment of 1999, 2000 and 2002, showing so many gaps and uncertainties in our knowledge on MGA." However, none of the experts have identified the gaps in evidence relating to MGA referred to by the EC. This is confirmed by the experts' responses to Question 62. Further, as noted by the Appellate Body, "the existence of unknown and uncertain elements does not justify a departure from the requirements of Articles 5.1, 5.2 and 5.3, read together with paragraph 4 of Annex A, for a risk assessment."[112]

107. Finally, the EC questions whether Dr. Boisseau can "assure the Panel that all the relevant and necessary scientific aspects about the safety of MGA have been completely and properly analyzed and assessed." Once again, the insinuation that Dr. Boisseau is responsible for providing an "assurance" to the Panel on melengestrol acetate appears to be nothing more than a thinly-veiled attempt to coerce Dr. Boisseau into changing his clear scientific opinions and honest review of the materials put forward by the EC in support of its ban. This is the very task he was charged with by the Panel. Further, as noted by the Appellate Body, "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[113] Rather the relevant analysis is whether the EC, in support of its provisional ban on melengestrol acetate, has adduced sufficient evidence to demonstrate that it has based its provisional ban on available pertinent information and that there is insufficient scientific evidence for the EC to conduct a risk assessment for MGA. The experts' responses demonstrate that the EC has failed to demonstrate either of these elements.

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[111] *See*, *e.g.*, Dr. Guttenplan Responses (Question 61), p. 13 ("[t]he [JECFA] assessment for melengestrol acetate seems sound.")

[112] Appellate Body Report, Australia – Salmon, para. 130.

[113] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

108. Question 36: The EC notes its agreement with Dr. Cogliano's response, but fails to cite to the previous sentence of Dr. Cogliano's reply: "[i]n my view, it is widely accepted that adverse effects arising from hormonal activities depend on the dose; that is, the level of effect depends on the level of exposure." Further, the EC concludes that Dr. Cogliano's response "is also consistent with the Appellate Body's 1998 decision in the Hormones case that a qualitative assessment of the risk is acceptable under the SPS Agreement." The United States addresses this overly-simplistic description of the Appellate Body findings at Section B.2 above. In addition, the United States notes that the experts have confirmed that the EC has not completed the four-steps of a risk assessment (including hazard characterization).[114]

109. The EC also cites Dr. Boobis' statement that "once a compound is identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action, no exposure is considered without risk." As has been made clear in Questions 19 and 20 above, Dr. Boobis has concluded that the evidence on the hormones, including estradiol 17β, does not indicate that they are in vivo DNA-reactive mutagens (Dr. Boobis concludes: "[t]here is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this. Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance.").

110. Question 37: The EC comment that "[b]oth Dr. Boisseau and Dr. Boobis appear to agree with the EC argument contesting Canada's position" on dose-response assessments is remarkable in light of the actual responses of the experts to the Panel's question. Dr. Boisseau: "JECFA has always established ADIs for veterinary drugs on the basis of a dose-response assessment." Dr. Boobis: "Codex and JECFA materials certainly require that a dose-response assessment should always be conducted as part of the risk assessment of a chemical agent (CAC, 2005; IPCS: EHC 70, 1987 and EHC 104, 1990; IPCS, 2005; WHO, 1996 and 2001)." (Emphasis added).

111. Question 38: Please see U.S. Comments on the Experts' Responses, Section C.4(c) for a discussion of Question 38 and sensitive populations. The EC comments that "it is not very uncommon in JECFA to use data from assays which are not yet properly validated." However, the EC provides no evidence to support this conjecture. For physiological levels of sex hormones in prepubertal children, JECFA used values from the literature which were validated as a prerequisite for publication in a peer-reviewed journal.[115] The EC also claims that "JECFA originally used the limit-of-detection as the 'real' level when they could not measure the levels." This statement by the EC is also false. In the peer-reviewed reference used by JECFA (Ansusingha *et al.*), the authors reported that the circulating concentration of estradiol 17β was

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[114] *See* Question 14 above.

[115] The reference cited in the 32nd JECFA Report for concentrations of estradiol 17β in prepubertal children is: Angsusingha K. et al. Unconjugated estrone, estradiol and FSH and LH in prepubertal and pubertal males and females. J Clin Endocrinol Metab 1974; 39:63-68.

detectable using their assay in every prepubertal child studied, and the limit of detection was not substituted for actual values.

112. The EC has relied on the Klein assay to make the claim that circulating levels of estradiol 17β in prepubertal children are 100-fold lower than previously estimated. However, the EC's support for the Klein assay appears to be waning. The EC notes, "[t]he real values for 17β-oestradiol in prepubertal children still remain to be properly documented." With this statement, the EC appears to recognize that the results of the Klein assay it has employed in its analysis are unreliable, not definitive and unvalidated. Dr. Boobis questions the validity of the Klein assay and suggests that significantly higher concentrations of estradiol 17β in prepubertal children measured by another sensitive bioassay (Paris *et al*., 2002) are more credible. The EC disagrees with Dr. Boobis' assessment on the basis that the Paris assay also detects, albeit with poor sensitivity, natural estrogens other than estradiol 17β (estrone and estriol). However, Paris *et al*. point out that relative to estradiol 17β, their assay is 1-2 orders of magnitude less sensitive to estrone and estriol. Therefore, concentrations of estrone and estriol in prepubertal children are not high enough to contribute to the estrogenic activity measured in this assay.

113. Finally, the EC comments that "[s]ince it is not possible to make the calculation on daily production rates without knowing the serum levels and the metabolic clearance rate in the most sensitive segment (children), and JECFA considers such data essential for determining an ADI, it must be accepted that JECFA cannot set the ADI and MRL before the values are known!" This is why safety factors are used by JECFA. In the case of estradiol 17β, the safety factors were very conservative (10-fold for sensitive populations and an additional 10-fold for inter-individual variation).[116]

114. Question 39: The EC asserts that it has performed a "quantitative assessment taking into account the lower endogenous production levels for pre-pubertal children from the most recent and reliable data." As demonstrated in the U.S. Comments on the Experts' Responses, the data relied on by the EC was generated via an unvalidated assay.[117] The EC concludes that Dr. Boisseau's response is "false", but fails to address the point made by Dr. Boisseau in his comment, *i.e.*, that "[t]his excess exposure of these sensitive populations needs to be assessed and compared with the exposure resulting from the daily consumption of meat from cattle which have not been treated with growth promoters, from other food and products of animal origin and from their own production of hormones." The EC presents no evidence of how it has assessed and compared these risks in its Opinions and thus fails to demonstrate that it has in fact conducted an exposure assessment for sensitive populations.

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[116] *See* Dr. Boobis Responses (Question 42), p. 39.

[117] *See* U.S. Comments on the Experts' Responses, Section C.4(c).

115. The EC "agrees with Dr. Sippell's assessment," regarding which the United States has already provided detailed comments,[118] and notes that he "demonstrates why there are a number of sources confirming the values mentioned by Klein et al, 1994 and 1999." To the contrary, the only "source" that Dr. Sippell provides to support the results of the Klein assay is the publication by Paris *et al*. However, as discussed in the U.S. Comments on the Experts' Responses at paragraph 66, the results of the Paris assay do not confirm the values reported by Klein *et al*. Instead, Paris *et al*. reported circulating levels of estradiol 17β that are at least an order of magnitude greater than those obtained using the Klein assay. It is important to note that concentrations of estradiol 17β in prepubertal children reported by Paris *et al*. Are much closer to the values used by JECFA than to the values reported by Klein *et al*.[119]

116. Question 40: As noted in Question 38 above, the EC's statement that "JECFA originally used the limit-of-detection as the 'real' level when they could not measure the levels" is pure speculation for which the EC provides no evidence. To the contrary, in the peer-reviewed reference used by JECFA,[110] the authors reported that the circulating concentration of estradiol 17 was detectable using their assay in every prepubertal child studied, and the limit of detection was not substituted for actual values. Also, the EC notes that "[t]he real values for 17β-oestradiol in prepubertal children still remain to be properly documented." With this statement, the EC appears to recognize that the results of the Klein assay it has employed are unreliable, not definitive and unvalidated.

117. As noted in Question 39 above, the Paris assay does not validate the Klein assay despite the EC's statement that "Dr. Sippell provides convincing explanations and arguments to accept as valid the results from the RCBA assay." The EC fails to note Dr. Boobis' conclusion that "[t]he reliability of the Klein et al assay has yet to be determined." The EC also fails to mention Dr. Boisseau entirely, who states that "[i]t would be important to know wether these new bioassays have been properly validated as this SCVPH Opinion says nothing about that and wether the data obtained with these methods for both men and women are also totally different from those obtained with the RIA methods."

118. Finally, the EC fails to note Dr. Boobis' ultimate conclusion which is that, even assuming the lower levels of circulating estradiol 17β proposed by Paris *et al*., the simple fact is that "exposure is via the oral route, and bioavailability by this route is very low (<5%) (Fortherby, 1996). In addition, very little of the absorbed hormone will be free, over 95% being bound to plasma proteins such as SHBG. Such binding reduces the biological activity of the hormone

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[118] *See* U.S. Comments on the Experts' Responses, Section C.4(c).

[119] The mean concentration of estradiol 17β in prepubertal boys in the study used by JECFA (Ansusingha *et al*. J Clin Endocrinol Metab 1974; 39:63-68) was 5 pg/ml. Corresponding values reported by Paris *et al*. and Klein *et al*. were 1.44 pg/ml and 0.08 pg/ml, respectively.

(Teeguarden and Barton, 2004). Hence, the JECFA ADI would appear to be appropriate for all groups of the population."

119. Question 41: The EC comments that the replies of Drs. Boisseau and Boobis are "not entirely convincing," and in support of this claim cites to alleged risks concerning "estradiol-17-esters and estradiol-alpha found in residues in treated steers." As noted by the United States in Questions 13, 17 and 28 above, the EC's suggestion that estradiol 17α is present in beef and may be further metabolized in the human consumer to catechol estrogens is weak for several reasons: (1) Maume *et al*.[111] demonstrated that estradiol 17α concentrations are elevated only in liver and kidney, but not muscle, following administration of a single implant (muscle is the tissue most often consumed); (2) the EC attempted but was unable to provide evidence estradiol 17α can be converted to catechol estrogens by human intestinal cells[112]; and (3) estradiol 17α does not appear to be carcinogenic[113] and thus does not fit into the EC's theory that estrogens are genotoxic carcinogens (via catechol metabolites).

120. The EC also concludes that "the most important studies available provide a bioavailability rate which is 10% or higher (see the 2nd EC Written Submission)." However, review of the section of the Second EC Written Submission which discusses bioavailability of hormone residues (paragraphs 123 to 124) reveals no information to support the statement that bioavailability of these residues is greater than or equal to 10%. In fact, as the U.S. has pointed out in its Comments on the Experts' Responses,[114] the EC has failed to provide any evidence to contradict the statement by Dr. Boobis indicating that the bioavailability of natural hormone residues < 5-10%. This statement is supported by several peer-reviewed publications.[115]

121. Question 42: The EC again attempts to dismiss the responses of Drs. Boobis and Boisseau because they have "not carried out any research themselves on these hormones and so have no specific expertise." The United States has addressed this unfounded objection at several points above. Drs. Boobis and Boisseau are intimately familiar with the workings of JECFA and are highly qualified to respond to the Panel's question (indeed, Drs. Boisseau and Boobis were initially proposed as experts by Codex and JECFA). The EC notes that the experts' responses are "very monolithic and one-sided", presumably because the responses disagree with the EC position on whether JECFA adequately took into account sensitive populations.

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[111] Exhibit EC-78.

[112] Exhibit EC-51C.

[113] Fritsche S. and Steinhart H. Occurrence of hormonally active compounds in food: a review. Eur Food Res Technol 1999; 209:153-179.

[114] *See* U.S. Comments on the Experts' Responses, paras. 27-30.

[115] *See* Dr. Boobis Responses (Question 43), p. 40.

122. The EC comments that the responses of Drs. Boisseau and Boobis "are based again on the assumptions that this hormone [estradiol 17β] is not genotoxic and that the rate of endogenous production by prepubertal children is correctly cited in the JECFA report." These are not "assumptions", however, but reflect the views of both experts on the state of the scientific evidence relating to estradiol 17β. Indeed, both Dr. Boobis and Boisseau have concluded, based on a review of the EC's Opinions, the science cited therein, and a review of relevant recent scientific literature that estradiol 17β is not genotoxic in vivo, nor would it be genotoxic at levels found in residues in meat from cattle treated for growth promotion purposes.[116]

123. The EC claims that "there are so many other reasons to believe that the JECFA evaluation is scientifically wrong, as explained above (old and unreliable data, etc.), [that] no reliance can be placed on the replies by these two experts." The United States has demonstrated at length above that the EC has failed to demonstrate that JECFA's evaluation is "scientifically wrong" and that the EC has failed to support its conclusions which diverge from those of JECFA with scientific evidence. Thus, the EC has failed, for purposes of Article 3.3 of the SPS Agreement, to maintain its measure (permanent ban on estradiol 17β), which allegedly results in a higher level of protection than that expressed in the JECFA standard, with a "scientific justification."

124. Question 43: The EC disagrees with Dr. Boisseau, who opines the estradiol 17β is "inactive orally" because, according to the EC "[t]his is simply factually wrong! Oestradiol 17β is routinely administered to humans as a powder or in the form of pills that are taken orally." In support of its argument, the EC cites to Lampit *et al*. However, 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. The EC comments that there are "no doubts that oestradiol-17β is orally active." As noted in Question 8 above, while it is true that estradiol 17β is administered orally for some indications, because its bioavailability is so low, very high doses are required to elicit the desired therapeutic effect. For example,

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[116] *See*, *e.g.*, Dr. Boobis Responses (Question 16), p. 20 ("[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity"; [t]he evidence is against any direct interaction of oestradiol or its metabolites with DNA."); Dr. Boobis Responses (Question 18), p. 22 ("[t]o reiterate, whilst there are reliable studies demonstrating the genotoxicity of oestradiol in certain in vitro tests, the evidence is against any genotoxicity in vivo.") (note that the EC's own guidelines on genotoxicity testing "require confirmation of an in vitro positive using an appropriate in vivo assay." *See* CVMP (2004). Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing, European Medicines Agency, London); Dr. Boobis Responses (Question 19), p. 22 ("[t]here is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this. Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance.") (Emphasis added); Dr. Boisseau Responses (Question 13), p. 11 ("[i]n conclusion, the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans.") *See also* Dr. Cogliano Responses (Question 18), p. 1 ("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.")

therapeutic doses of estradiol 17β for oral administration range from 0.5 - 4.0 milligrams,[117] or 10,000 - 40,000 times higher than the 30-50 ng/person/day derived from eating beef from cattle treated with estradiol 17β for growth promotion purposes. In addition to high doses, orally administered estradiol 17β are manufactured as micronized formulations (particle size < 10 microns) to further increase bioavailability. Even after micronization, the bioavailability of a 2 mg dose of estradiol 17β is still only about 5%.[118]

125. The EC also notes that it has provided "credible recent evidence" that "the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is taken into account." However, as noted in Question 41 above, review of the section of the EC's Second Written Submission which discusses bioavailability of hormone residues (paragraphs 123 to 124) reveals no information to support the statement that bioavailability of these residues is greater than or equal to 10%. In fact, as the United States has pointed out in its Comments on the Experts' Responses,[119] the EC has failed to provide any evidence to contradict the statement by Dr. Boobis indicating that the bioavailability of natural hormone residues < 5-10%. This statement is supported by several peer-reviewed publications.[120]

126. The EC "agrees with the summary of this question as stated by Dr. Guttenplan." However, as addressed by the United States in paragraph 29 of its Comments on the Experts' Responses, Dr. Guttenplan appears to be simply restating the EC's conclusions, which have been shown to be erroneously based on three studies that do not even address bioavailability.

127. The EC asserts that "[n]either Dr. Boisseau nor Dr. Boobis provide a specific reply to [Dr. Guttenplan's reply concerning prepubertal children]," a statement that the United States finds perplexing based on a review of Dr. Boobis' very detailed reply to the question of whether estradiol 17β in beef presents a risk factor for prepubertal children.[121] Indeed, Dr. Boobis takes into account the possibility that circulating levels of estradiol 17β are lower than previously estimated. Using this assumption, together with the well-supported conclusion that bioavailability of estradiol 17β is very low (< 5%), Dr. Boobis shows very convincingly that consumption of beef from cattle treated with estradiol 17β for growth promotion does not approach the ADI and thus does not pose a risk to prepubertal children.

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[117] *See* 2002 Report on Carcinogens. (Exhibit US-26).

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

[119] *See* U.S. Comments on the Experts' Responses, paras. 27-30.

[120] *See* Dr. Boobis Responses (Question 43), p. 40.

[121] *See* Dr. Boobis Responses (Question 40), p. 37-39.

128. Finally, the EC notes that "the bioavailability of the three synthetic hormones has not been determined by JECFA." However, the EC fails to note that, because the bioavailability is unknown, JECFA made no correction for bioavailability in its assessment (*i.e.*, it assumed 100% bioavailability). This is obviously a very conservative approach to this issue, since it is unlikely that the bioavailability of any of the synthetic hormones would be 100% (and even if it were, this potential was taken into account). Ethinyl estradiol (a synthetic estrogen), for example, is 55% bioavailable. Thus, the EC's attempt to cast doubt on the JECFA risk assessments and standards relating to those hormones by arguing that the bioavailability of the three synthetics is unknown is unconvincing.

129. Question 44: The EC cites Dr. Boisseau's opinion that "Codex did not adopt any guideline for GVP aimed at minimizing the occurrence of veterinary drug residues in animal derived food" as supporting its argument.[122] However, the EC does not clarify to what argument it is referring. The United States notes that Dr. Boisseau's statement that Codex has not adopted a guideline on GVP is unexceptional, and reiterates that the essential analysis is whether the EC, in its purported risk assessment, has properly examined and evaluated a risk from the failure of good veterinary practices (per Articles 5.1 and 5.2 of the SPS Agreement). The EC appears to accept that it must evaluate this risk, if the assumption of failure of controls is to be a mainstay of its purported assessment, by citing to guidance from the Appellate Body.

130. As the United States has demonstrated, the EC has failed to assess a risk from failure of controls.[123] The experts have confirmed this fact.[124] The EC notes that "there is an important difference between the theoretical assumption of respecting [good veterinary practices] and real life," but has simply not evaluated the risk of failure of good veterinary practices, nor has it even demonstrated through scientific evidence that, save for the most unrealistic misuse scenarios (extreme overdosing), residues of the hormones would reach violative levels.[125]

131. Question 45: The EC cites Dr. Boisseau for the proposition that Codex recommendations "are only meaningful in countries where GVP are effectively implemented." This is so because,

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[122] Note the failure to complain about Dr. Boisseau's laboratory experience in this instance.

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

[124] *See* Dr. Boobis Responses (Question 48), p. 42 ("There was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies. Indeed, the SCVPH (2002) simply noted that 'Therefore, these data have to be considered in any quantitative exposure assessment exercise', without undertaking such an exercise.") (Emphasis added); Dr. Boisseau Responses (Question 48), p. 24 ("the European Communities did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses.") (Emphasis added).

[125] *See generally* Dr. Boobis Responses (Question 62), pp. 50-52; *see* U.S. Comments on the Experts' Responses, Section C.6; U.S. Rebuttal Submission, Section II.B.4.

as noted by the United States in its Comments on the Experts' Responses at footnote 222, approvals of or standards relating to veterinary drugs (or any substance for that matter) are not premised on the notion of misuse. Any drug can be misused, and most drugs can be harmful if consumed at extremely high, unrealistic levels. If misuse were used as a baseline for veterinary drug approvals, no drugs would ever be approved. However, as noted by the Appellate Body, for purposes of an SPS measure, a Member may take misuse or failure of controls into account as part of their basis for that measure, but they must actually evaluate or assess that risk. The United States has demonstrated at several points in its Rebuttal Submission and Comments on the Experts' Responses that the EC has failed to evaluate this risk.[126] The experts have confirmed this fact.[127] The experts have further confirmed that the scientific evidence relied on by the EC for its conclusion that artificial misuse scenarios will lead to violative levels of hormone residues does not support that conclusion.[128]

132. As noted by the United States in its Comments on the Experts' Responses at paragraph 101, the issue of conditions of use, and whether the EC has evaluated the risk from misuse, is essential to a determination of whether it has based its permanent ban on estradiol 17β on a risk assessment within the meaning of Articles 5.1 and 5.2 of the SPS Agreement and whether its provisional ban on the five other hormones is based on available pertinent information within the meaning of Article 5.7 of the SPS Agreement. The fact that the EC has raised the issue of misuse[129] and devoted considerable resources to demonstrating the potential consequences of misuse implies that it already recognizes that there are conditions under which residues of the six hormones used for growth promotion are safe. In other words, if, as argued by the EC, the six hormones pose a risk at levels found in residues in meat from cattle treated according to good veterinary practices, then why has the EC tried to refocus attention on the specter of misuse? The only germane question then would be whether there are particular conditions of use under which there would be a health risk.

133. Question 47: The EC comments that Dr. Boisseau's response is "partially false", because he has concluded that "the [EC] did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the [EC] took into account relevant control mechanisms with respect to GVPs in place in the USA." The simple fact is that the experts have reviewed the EC's Opinions and the studies cited therein, and have determined that the EC has failed to assess

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

[127] *See* Dr. Boobis Responses (Question 48), p. 42; Dr. Boisseau Responses (Question 48), p. 24.

[128] *See generally* Dr. Boobis Responses (Question 62), pp. 50-52; *see* U.S. Comments on the Experts' Responses, Section C.6; U.S. Rebuttal Submission, Section II.B.4.

[129] *See*, *e.g.*, Replies to Questions from the Panel after the First Substantive Meeting by European Communities, para. 91.

this risk.[130] Insofar as Dr. De Brabander has spoken to the issue of whether or not the EC's Opinions adequately evaluate the risk from misuse, the United States addresses his comments in its Comments on the Experts' Responses at Section C.6.

134. The EC claims that the "evidence available does show that such misuse or abuse occurs frequently, because these hormones are administered in combinations and the farmers have incentives to apply multiple doses." Each of these conclusions is speculative and unsupported by the evidence presented. The experts' responses have confirmed this fact (note that none of the experts cites to any of this purported evidence of "frequent" misuse), and the United States has demonstrated at great length in its Rebuttal Submission at paragraphs 54-66 and Comments on the Experts' Responses at paragraphs 105-106 that there is in fact great disincentive for commercial feedlot operators to misuse growth promoters. Programs administered by the U.S. Government include setting safe levels for veterinary drugs; monitoring for violative residues; and inspection of meat at the ante-mortem, post-mortem and processing stages. As large commercial operations, U.S. feedlots have great incentive to comply with the regulations set and enforced by USDA and the FDA. In support of its claim that "farmers have incentives to apply multiple doses" the EC has cited in previous submissions to a document entitled "Beef Cattle Implant Update" authored by Dr. Dee Griffin (Exhibit US-27). The United States has submitted a letter from Dr. Griffin in which he explains that this document does not support the conclusions taken from it by the EC, and confirms that there is absolutely no incentive (either economic or legal) to misuse growth promoting implants.[131]

135. Question 48: The EC argues that the responses of Drs. Boisseau and Boobis are misguided because "as the [EC] has explained several times in previous questions, [a quantitative assessment] is not required under the SPS Agreement as interpreted by the Appellate Body." The United States has addressed both: (1) the notion that experts should be taking legal considerations into account, and (2) the EC's overly simplistic reading of the Appellate Body statement above.[132] In any event, the EC does not rely on its assertion that it may just produce a qualitative assessment, but instead states that "the [EC] has nevertheless performed a quantitative dose-response assessment in particular with regard to prepubertal children." Thus, it is patently unclear how on the one hand the EC can dismiss the comments of the two experts for analyzing the EC assessment as though it should have been a quantitative assessment while on the other claiming that it has conducted just such a quantitative assessment.

136. The experts do not agree with the EC that it has conducted a quantitative assessment. Dr. Boobis: "There was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies.

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[130] *See* Questions 44-46 above.

[131] *See* Letter from Dr. Dee Griffin explaining results of Beef Cattle Implant Update. (Exhibit US-28).

[132] *See*, *e.g.*, Section B.2.

Indeed, the SCVPH (2002) simply noted that 'Therefore, these data have to be considered in any quantitative exposure assessment exercise', without undertaking such an exercise." Dr. Boisseau: "the European Communities did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses." As described in detail in the U.S. Comments on the Experts' Responses, Dr. De Brabander does not appear to offer an opinion as to whether the EC has indeed assessed risks to human health from misplaced implants or improper administration.[133]

137. The EC also claims that "it is obvious that the higher levels of residues that will inevitably result from misuse or abuse of these hormones will also exceed the ADIs and MRLs recommended by JECFA." However, as demonstrated by the United States in its Rebuttal Submission[134] and confirmed by Dr. Boobis (the only expert to specifically analyze the misuse studies conducted by the EC), this conclusion is unsupported by the scientific evidence. Dr. Boobis (Question 62): "the data generated by the EU research in question [*i.e.*, concerning artificial misuse scenarios] do not provide any indication that it is not possible to conduct a risk assessment of the hormones used as growth promoters. Nor do they provide any indication that even such misuse or abuse as investigated gives rise to undue risk from the resultant residues, as intake would only very rarely exceed the ADI and then only on a rare occasion."

138. In short, insofar as the EC's "risk assessment" for estradiol 17β relies on the conclusion that the scientific evidence demonstrates that misuse is likely to occur and that residue levels posing a risk to human health will result, that assessment is not a "risk assessment, as appropriate to the circumstances" within the meaning of Article 5.1 and 5.2 of the SPS Agreement. Further, insofar as the EC's provisional bans are allegedly based on "available pertinent information" regarding misuse or residue levels posing a risk to human health resulting from misuse, those bans do not satisfy the conditions of Article 5.7 of the SPS Agreement. Similarly, insofar as the EC's provisional bans are premised on alleged insufficient scientific evidence to conduct a risk assessment, those bans do not satisfy the conditions of Article 5.7 of the SPS Agreement.

139. Finally, the EC comments that Dr. Boobis' reference to "probability" of a risk is inappropriate in light of the Appellate Body's interpretation that a Member must identify the "possibility" of a risk. The United States addresses the EC's interpretation of the Appellate Body's decision at several points above.[135] However, the distinction between "probable" and "possible" is irrelevant to an analysis of what the EC has or has not accomplished in its "risk assessment" in light of the fact that it has asserted that "the [EC] has [] performed a quantitative

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[133] *See* U.S. Comments on the Experts' Responses, Section C.6.

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

[135] *See*, *e.g.*, Section B.2.

dose-response assessment," which would by its very nature account for probability. The experts do not believe that the EC has completed such an assessment.

140. Question 49: The EC comments that less trade restrictive measures "apply only for the countries that would be prepared to assume that the possible risk would not undermine their chosen level of protection." The EC's statement presumes that the WTO Member in question has conducted a risk assessment, upon which it has based a measure that achieves its appropriate level of protection. The EC has not accomplished this task.

141. Question 50: The EC asserts that "if GVP is not respected, then the importing country should have the right to restrict imports, even with a total ban." The United States demonstrates that the fact that the EC has not addressed the risk of failure of controls or good veterinary practices in its comments above. Again, the experts have confirmed this point. The United States also reiterates that a focus on good veterinary practices and their potential failure by its very nature marks an acceptance that the hormones do not pose a risk to consumers when used in cattle for growth promotion purposes (or conversely, that the EC has failed to produce a "risk assessment" or scientific materials demonstrating such a risk).

142. The United States also notes with interest the EC's agreement with the comments of Dr. De Brabander, who is of the opinion that "there are no other measures possible to the [EC], other than a complete ban, which could address risks arising from misuse and failure to follow good veterinary practices." Dr. De Brabander's response appears to indicate that there is no way to control the use of these substances other than a ban. If this is so, and a complete ban is the only possible remedial measure, then the controls currently employed by the EC for the administration of the hormones to cattle are also inadequate. Further, as demonstrated by the United States, a ban is not, as it appears to have been cast by Dr. De Brabander and the EC, a iron clad assurance that no misuse will ever occur. This conclusion is supported by evidence of an active, illegal black market for the use of hormones in the EC, which chose to impose a ban on their use.[136]

143. Question 51: The EC fails to mention that Dr. Boisseau notes that "the European Communities did not conduct any quantitative risk assessment for growth promoters, [and] it is [therefore] not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses." The United States also notes that Dr. Boobis has provided a detailed analysis of the studies relied on by the EC as evidence of misuse leading to residue levels higher than Codex MRLs or ADIs – he concludes that the EC materials do not threaten these levels even under extreme circumstances.[137] The EC states that it "agrees" with Dr. De Brabander's opinion.

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[136] *See* U.S. Rebuttal Submission, Section II.B.4.

[137] *See* Dr. Boobis Responses (Question 62), pp. 50-52; *see also* U.S. Rebuttal Submission, paras. Section II.B.4.

The United States addresses the notion that JECFA's data is "older" and therefore inadequate at paragraphs 22, 92, and 102-104 above, and paragraphs 92 and 111 of its Comments on the Experts' Responses. The United States addresses the inapplicability of the other conditions raised by Dr. De Brabander to the situation at hand (*i.e.*, ban on imported meat) at Section C.6 of its Comment on the Expert Responses.

144. Question 52: The EC's comments on Question 52 appear to distract from the Panel's question, which is "[d]o the risk assessment of the [EC] or any other scientific materials referred to by the [EC] demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes." The EC describes the responses of Drs. Boobis and Boisseau as "scientifically incorrect", yet fails to provide any scientific evidence to counter the opinions of these two experts (opinions which appear to be based on a thorough review of the materials put forward by the EC in alleged support of its ban).

145. Dr. Boisseau states: "the European Communities did not carry out, strictly speaking, a risk assessment but provided scientific data and hypothesis supporting its worries regarding the safety of these six hormones for human health." He also concludes that: "the European Communities did not demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth promotion purposes." The EC's only response to these conclusions is to tout the conclusions of its own materials, averring that it has actually conducted a risk assessment in the form of its 1999, 2000 and 2002 Opinions. The experts do not agree with the EC's opinion of these materials. The EC claims that Dr. Boisseau must not have "properly examined" its Opinions because he has concluded that they do not constitute risk assessments. To the contrary, Dr. Boisseau's answers are detailed and indicate a very thorough reading of the EC's Opinions and other materials.

146. The EC attempts to dismiss Dr. Boobis' response due to the fact that he concludes that "all of the major reviews in this topic (*i.e.*, genotoxicity) have concluded that whilst there are data gaps, there is no evidence that low level exposure is causing harmful effects in humans," and "[t]he carcinogenic effects observed are entirely consistent with a hormonal mode of action that exhibits a threshold that would be well above the intake arising from consumption of meat from treated cattle." The EC focuses on the reference to data gaps as in some fashion supporting its decision to permanently ban the import of meat from cattle treated with estradiol 17β for growth promotion purposes. The EC fails to emphasize: (1) Dr. Boobis' conclusion that "there is no evidence that low level exposure is causing harmful effects in humans; (2) Dr. Boobis' response to the Panel's question concerning any potential data gaps (Question 62) (data presented by the EC "do not demonstrate any important gaps, insufficiencies and contradictions in the scientific information used by JECFA"); (3) Dr. Boobis conclusions to other Panel questions relating to genotoxicity (*e.g.*, Question 18 ["the evidence is against any genotoxicity in vivo."]); (4) relevant discussion from the Appellate Body ("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.")[138]; and (5) relevant discussion from the compliance panel in *Japan – Apples (21.5)* (scientific conclusions reached in a risk assessment must actually be supported by the scientific materials cited therein).[139]

147. The EC agrees with Dr. Guttenplan's comments. As noted by the United States in Question 43 above, however, contrary to Dr. Guttenplan's conclusion, use of hormones according to good veterinary practice to promote growth in cattle will not result in residue levels that exceed relevant ADIs or FDA's safe levels.

148. Question 53: The EC notes, regarding Dr. Guttenplan's response, that "this is still another kind of uncertainty that should be taken into account by the Panel in deciding whether the evaluations by JECFA are credible and reliable." The United States reiterates that the EC has adopted a permanent ban on estradiol 17β based on what it claims is a risk assessment, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement. Theoretical uncertainty may not serve as the basis for such an assessment.[140] Further, the EC fails to note Dr. Guttenplan's conclusion that "because the concentrations of all of the hormones in beef are so low, [] they would be unlikely to affect the potency of estrogen." Finally, Dr. Guttenplan notes that "no experiments on effects of combinations were performed, so some uncertainty exists there." If the scientific evidence does not, through a lack of study, demonstrate a risk or support the conclusion that combinations with estradiol 17β, the EC may not rely on this conclusion in its "risk assessment" within the meaning of Article 5.1 of the SPS Agreement.[141]

149. The EC also appears to ignore the following conclusion from Dr. Boisseau: "[c]onsidering that it has been established that progesterone and testosterone are not genotoxic, it is not likely that the testing of combinations of progesterone or testosterone with oestradiol-17β would have led to synergistic effects compared with those obtained from these individual substances."

150. Question 54: As noted in Question 16 above, the EC claims that Codex has set a "qualitative" appropriate level of protection, whereas the EC has set a "quantitative" level of protection. Yet the EC then argues that it achieves this "quantitative" level of protection with a "qualitative" risk assessment. The logic of the EC's argument does not follow. Further, the EC appears to have recast its level of protection as one of "no risk" as opposed to "no additional risk." A "no risk" level of protection (assuming that the EC were actually able to demonstrate a

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[138] Appellate Body Report, para. 167. Recall that the EC claims to have imposed its permanent ban on estradiol 17β based on a risk assessment within the meaning of Article 5.1.

[139] *See* Panel Report, Japan – Apples (21.5), paras. 8.145-8.146.

[140] *See* Appellate Body Report, para. 167.

[141] *See* Panel Report, Japan – Apples (21.5), paras. 8.145-8.146.

risk to human health from residues of the hormones in its Opinions) would presumably capture, and require the cessation of, several existing uses of the hormones in cattle in the EC as well as the consumption of numerous foods containing any of the six hormones.

151. In the event that the EC's appropriate level of protection is still one of zero additional or additive risk from the use of growth promoting hormones in meat, as it alleged in its 1999 Opinion, the United States would note the following expert consensus expressed in response to Question 55 (recall the following statement by the EC: "the [EC] has [] performed a quantitative dose-response assessment in particular with regard to prepubertal children."[142]): Dr. Boobis: "[t]he EC Opinions and other materials referred to by the EC do not quantify the extent to which residues of the hormones contribute to aggregate exposures or cumulative exposures to multiple hazards"; Dr. Guttenplan: "[i]n general the EC do not attempt to evaluate 'the additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'"; Dr. Boisseau: "[t]he European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute to 'additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'."

152. The EC fails to note the following comment from Dr. Guttenplan: "[t]he question of what level of risk has not been addressed by the EC." The EC also states, "[f]or the benefit of Dr. Guttenplan" that "Codex has not set an ADI or an MRL for MGA yet." (Emphasis in original). JECFA, on the basis of its risk assessment on MGA, recommended an ADI for melengestrol acetate at its 54th Meeting in 2004. JECFA recommended MRLs for melengestrol acetate at its 66th Meeting.

153. Question 55: The EC requests that the Panel "disregard [the comments of Drs. Boisseau and Boobis] because they are purely theoretical and for the additional reason that they come from two experts who have never done any specific research on these hormones nor have they ever published something on these substances." The United States has addressed similar objections by the EC in its comments above. In this instance, the United States would also note that the Panel's question is one of interpreting or analyzing materials and conclusions drawn in a "risk assessment." Both experts are eminently qualified in conducting, interpreting and analyzing risk assessments and Dr. Boobis has published on matters of risk assessment theory.[143] The EC's assertion that these experts are not qualified to respond to the Panel's questions is spurious, and is a weak attempt to distract from the responses of Drs. Boobis and Boisseau, *i.e.*, that the EC has not evaluated the "additive risks" in its Opinions or scientific materials.[144]

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[142] EC Comments on the Experts' Responses (Question 39).

[143] *See Curriculum Vitae* of Drs. Boobis and Boisseau.

[144] The comments of Drs. Boisseau and Boobis are quoted in Question 54 above.

154. The EC notes that Dr. Guttenplan "would have liked to see much more evidence in the 1999 SCVPH assessment." The United States is surprised that the EC has put this comment forward in support of its arguments. One would think, particularly in an instance where a hormone such as estradiol 17β has been permanently banned on the basis of a purported risk assessment, that the EC would be more hesitant to trumpet the lack of evidence contained in the "risk assessment." Finally, the EC fails to note Dr. Guttenplan's ultimate conclusion, which marks a consensus with Drs. Boobis and Boisseau: "[i]n general the EC do not attempt to evaluate 'the additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'."

155. Question 56: The EC notes its disagreement with the response of Drs. Boobis and Boisseau that JECFA did in fact consider "additive risks" from the other five (provisionally banned by the EC) hormones. The EC simply restates its own opinion of the matter and speculates that Dr. Guttenplan would have agreed with the EC but that "words seem to be missing from his reply." Neither of the EC's comments amount to evidence, particularly the latter since this is not meant to be an exercise where the parties put their own words in the experts' mouths and claim that the experts would support their positions. Indeed, the EC's claim to powers of extrasensory perception may be as scientific as the EC measures at issue in this dispute.

156. The words actually contained in Dr. Guttenplan's response read as follows: "I could find assessment of additive risks of the hormones in the documents." This response marks consensus with the opinions of Drs. Boobis and Boisseau. (Dr. Boobis: "JECFA/Codex did consider aggregate risk from exposure to the natural hormones where present as residues in meat from treated cattle. Such exposures were considered to represent a trivial increase in overall exposure to hormonally-active material from other exogenous sources and in particular from endogenous sources (JECFA, 2000)." Dr. Boisseau: "JECFA/Codex considered in its risk assessment of the natural hormones such 'additive risks' and concluded that, given the wide margin of safety between the maximum estimated intake of residues for the these hormones and the corresponding established ADIs, that there was no risk for consumers' health associated with the estimated ingestion of these residues.")

157. The EC argues that "it has clearly been shown that the effects from exposure to different estrogens are additive . . . [t]hus any additional dose will lead to an increased effect." In support of this conclusion, the EC cites a study by Rajapakse *et al*. However, the Rajapakse paper reports that a heterogenous mixture of 11 estrogenic chemicals exhibited additive effects with estradiol 17β in a yeast-based reporter assay. The relevance of this study to the dispute is questionable because a yeast-based assay was used to measure estrogen activity, and the capacity of yeast-based assays to accurately reflect physiological effects of hormones in mammalian cells in vivo (*e.g.*, humans) has not been demonstrated.

158. The EC also notes that "the additive risk needs to be carefully evaluated. For instance, trenbolone as such has a complex hormonal activity (at the same time progestin, androgen and

glucocorticoid)." This comment appears to presuppose that JECFA did not engage in such a careful evaluation. The experts have confirmed, to the contrary, that JECFA did in fact evaluate these additive risks. Further, the EC has not provided scientific evidence to support the claim that trenbolone mimics the biological effects of glucocorticoid. In fact, there is evidence in the literature that trenbolone exerts antiglucocorticoid activity (Meyer H. Biochemistry and physiology of anabolic hormones used for improvement of meat production. APMIS 2001; 109:1-8). With respect to progestin, one of the EC's "17 Studies"[145] provided evidence that 17β-TBOH, the primary metabolite of trenbolone found in bovine muscle tissue, binds to the bovine progestin receptor. However, binding of trenbolone and its metabolites to the human progestin receptor was not investigated, and it must be emphasized that hormone binding in vitro is not equivalent to demonstrating that the hormone actually exerts receptor-mediated effects in vivo.

159. Question 57: Rather than commenting on the responses of Drs. Boisseau and Boobis, the EC questions the validity of the question, and notes that it is irrelevant. The EC apparently bases this conclusion on the fact that the "Appellate Body did not find any violation from the use of some of these hormones for therapeutic or zootechnical purposes." The EC does not provide any citation or context for this statement, and it is therefore unclear how it makes the Panel's question "irrelevant." Further, as noted above, the experts do not provide advice on legal matters, or evaluation of measures under the SPS Agreement. Rather, they assist a panel by providing advice and opinions on technical details of the dispute, thereby permitting the panel to reach these legal conclusions. One of the technical or scientific details at issue is the EC's argument, or assertion, that estradiol 17β is genotoxic. This is a fundamental assertion made by the EC in support of its ban, as is evidenced by the sheer number of times the EC refers to the genotoxic potential of estradiol 17β in its responses. The experts have, time and again, indicated that estradiol 17β is not genotoxic at levels found in residues in meat from cattle treated for growth promotion purposes.

160. Dr. Boobis concludes: "[t]o my knowledge no account is taken of hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic purposes, by the EC in its assessment of the aggregate or cumulative effects of the hormones in meat from cattle treated for growth promotion." Dr. Boisseau notes:

> The European Communities thinks that, given the conditions of theses uses of oestradiol-17β (limited number of treated animals, limited use in the life of these animals and very low probability to see these animals slaughtered after treatment), the exposure of consumers to oestradiol-17β residues resulting from these uses can be considered as negligible. If this EC assumption can be accepted, it raises nevertheless a problem of principle as it represents an exception regarding the very strict position of EC stating that it is not possible to accept any increase of the exposure of consumers to oestradiol-17β residues. As soon as the European Communities accepts to considers these residues

[145] Exhibit EC-15.

> resulting from these therapeutic and zootechnical use of oestradiol-17β as negligible, it enters in a quantitative, or at least in a semi quantitative, exposure assessment procedure for these oestradiol-17β residues and, starting from that, it has no good reason to object to consider a wider exposure assessment covering all the residues resulting from the different sources of oestradiol-17β.

161. The EC agrees with the conclusion of Dr. Guttenplan. The United States notes that Dr. Guttenplan's opinion, that zootechnical or therapeutic use would "not constitute a hazard for public health" appears to indicate that he is of the opinion that low levels of the hormones are not genotoxic. This comports with his opinion that an adverse effect is " unlikely if good veterinary practices are followed."[146]

162. Question 58: The EC's comments fail to address the responses of the experts. Dr. Guttenplan: "[t]his is indeed a very weak statement by the EC." Dr. Boobis: "[w]ithin quite broad limits, higher exposure would not result in any increase in risk." Dr. Boisseau: "[t]he European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute to 'additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'." The EC cites again to the 2002 Report on Carcinogens, which has been discussed in detail by the United States in its comments on the EC's comments on Question 12 above and in its Rebuttal Submission.[147] As demonstrated in the U.S. comments above, the EC has not in fact "shown that the level of residue formation in meat can be significantly higher and may contain residues from different metabolites."

163. Question 59: The EC notes "the different views which the replies of the scientists display on this critical question." The United States did not observe much of a difference of views amongst the experts, however. In fact, the United States notes a consensus in the experts' responses that, per the Panel's question, the EC has failed "to identify any adverse effects on the immune system from the consumption of meat from treated cattle with the growth promoting hormones at issue." Dr. Boobis: "[t]he evidence on immune effects of hormones such as oestradiol referred to by the EC does not identify any adverse effects on the immune system from consumption of meat from treated cattle. In general, clear evidence for immune effects were observed only at high doses." (Emphasis added). Dr. Guttenplan: "[n]o definitive studies have related intake of meat from hormone-treated animals to the above disorders." Dr. Boisseau: "as these data have not been used by the European Communities to conduct any quantitative risk assessment likely to establish, for these effects associated with the hormonal properties of growth promoters, thresholds and ADIs different from those proposed by JECFA, it is not possible to conclude that this scientific evidence allows to identify any adverse effects on the

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[146] Dr. Guttenplan Responses (Question 15), p. 4.

[147] *See* U.S. Rebuttal Submission, paras. 38-40.

immune system associated with the consumption of meat from cattle treated with the growth promoters at issue." (Emphasis added).

164. The EC also comments that the real question is not the one asked by the Panel, but "the degree of confidence by which the United States and Canada (and JECFA) can ensure [*sic*] the Panel that such adverse immune effects are not possible to occur in meat treated with these hormones for animal growth promotion. The [EC] thinks that they have failed to do so to the required standard of proof." This statement is flawed for several reasons. First, the EC, as the Member imposing a ban on meat and meat products, bears the burden of proof of demonstrating that its ban comports with its obligations under the SPS Agreement. The United States has presented more than sufficient argument and evidence on each of the scientific points raised by the EC to demonstrate that its ban is not, in fact, sufficiently warranted or reasonably supported by a risk assessment within the meaning of Article 5.1 of the SPS Agreement. Further, the United States has presented more than sufficient argument and evidence to demonstrate that the EC's provisional ban does not satisfy the EC's obligations under Article 5.7 of the SPS Agreement because there is sufficient scientific evidence for the EC to have conducted a risk assessment for each of the five hormones and the EC has failed to base its provisional ban on available pertinent information, all of which indicates that the five hormones do not pose a risk to human health when used as growth promoters in cattle. In other words, the United States has discharged its burden of proof in this dispute.

165. Second, the notion that the United States or JECFA must assure the EC that there is no risk of adverse effects from the use of the five hormones is simply a flawed attempt to distract from the issue at hand. As noted by the Appellate Body, "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[148] In other words, it is impossible to prove the absolute negative, despite the EC's demand for such proof from the United States and several of the experts. This is why Members, in imposing trade restrictions, must adduce evidence and evaluation of an actual risk against which their restriction or measure mitigates. The United States and JECFA have conducted risk assessments and concluded that the hormones do not pose a risk to consumers when used as growth promoters in cattle. That is why the United States does not, like the EC, impose a ban on the importation and sale of beef from treated cattle. The EC chooses to ban importation of this same beef. Therefore, the relevant analysis is whether the EC, in support of its provisional ban on meat from cattle treated with these hormones, has adduced sufficient evidence to demonstrate that it has based its provisional ban on available pertinent information and that there is insufficient scientific evidence for the EC to conduct a risk assessment for the hormones. The experts' responses demonstrate generally that the EC has failed to demonstrate either of these elements. The experts' responses to Question 59 specifically indicate that the EC's conclusion that immune or other adverse effects from use of the five hormones as growth promoters in cattle is scientifically baseless.

[148] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

166. Question 60: Citing to one of its "17 Studies",[149] the EC states that residues of MGA detected in U.S. beef were "much higher than the levels which should have been normally expected." However, the study that the EC refers to does not report actual residue levels in U.S. beef, but is one in a series of studies in which the EC deliberately overdosed cattle with MGA. The EC may have intended to cite to another of its "17 Studies"[150] in which the author reports that measurement of MGA in 103 U.S. beef samples "revealed MGA at trace levels in about 75 percent of the samples." No quantitative data are provided in this report, and there is no suggestion that the "trace levels" were violative according to U.S. tolerance levels. Therefore, the EC has failed to provide any evidence to support its claim that MGA is conducive to misuse or is administered in a manner that would result in unsafe residue levels in U.S. beef.

167. Citing again to one of its "17 Studies"[151] in which a misuse scenario was created for MGA, the EC notes that MGA has a "boosting effect" on residues of estradiol 17β in meat. It is true that this study demonstrated a 2.6-fold increase (not 3-fold as suggested by the EC) in estradiol 17β concentrations in fat following treatment with the FDA-approved dose of MGA. This is not surprising in light of the fact that MGA, at low concentrations, increases ovarian estradiol 17β secretion via effects on hormone negative feedback to the hypothalamus and pituitary gland. However, it should be noted that: (1) the results of this study are preliminary due to the limited number of animals used (only 2-4 animals per treatment group), and (2) the mean concentration of estradiol 17β in fat following MGA treatment (26 ppt) is 19 times lower than the U.S. tolerance (480 ppt).[152] Again, the evidence put forward by the EC simply fails to substantiate its claim that the use of MGA according to good veterinary practices results in hormone residues above the levels that have been determined to be safe for human consumption.

168. The EC's comment that it is interesting that the United States has used melengestrol acetate since the 1970s but that JECFA only evaluated MGA until 2000 is a *non sequitur*. The approval of MGA in the U.S. domestic market has no bearing on where and when JECFA was "seized of a request" to evaluate MGA. As noted above, JECFA has set an ADI (62nd Meeting) and proposed an MRL (66th Meeting) for MGA.

169. The United States has reviewed the materials put forward by the EC "following the Appellate Body 1998 hormones decision" and did not find any evidence of a risk from melengestrol acetate when used as a growth promoter in cattle. The United States discussed these studies in detail in its Rebuttal Submission. The experts reviewed these studies and concur with the opinion of the United States. Dr. Boobis: even "whilst [misuse] would lead to increased exposures, it is still unlikely this would exceed the ADI, and certainly not for any

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[149] Exhibit EC-16.

[150] Exhibit EC-19.

[151] Exhibit EC-16.

[152] *See* 21 C.F.R. § 556.240.

period of time. It is also an unlikely occurrence in view of the way in which the hormones are used and controlled." Dr. Guttenplan: "[t]he potential for excessive exposure to MGA exists by both routes (oral and implantation), but it cannot be stated and I am not aware of which route is more likely to contribute to high levels in meat." Dr. Boisseau: "the scientific evidence referred to by the European Communities does not identify and evaluate wether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives or implanted." The United States notes that, apart from its general conclusion that its studies support its ban on MGA, the EC fails to provide any specific discussion as to how or why this is actually so. Rather, the EC simply complains that the experts must not have read its materials.

170. The EC provides commentary on levels of residues in the event of non-removed implants. The United States has provided lengthy discussion of how implants are injected into the ears of cattle, that those ears are then discarded, and that ante- and post-mortem inspections ensure that the implants are not entering the food chain.[153] The EC's commentary speculates that an ear with an intact implant will enter the food chain. Again, this is nothing more than a paper exercise, and there is no evidence that this event will occur. The EC dismisses Dr. Boobis' response as "unfounded." However, the United States notes that Dr. Boobis has engaged in a detailed review of the materials underpinning the EC's ban, and has based his conclusion on the results of these very materials.[154] The United States reached the same conclusion after review of the scientific materials put forward by the EC.[155]

171. Question 61: The EC attempts to dismiss the opinion of Dr. Boisseau because "he has not done nor published any work on these hormones." As noted at several points above, this is not a legitimate reason for dismissing of an experts' opinion, nor is it a criteria that the EC has applied across the board with other experts (or even with the same expert, depending on the answer).

172. The EC questions the "objectivity and impartiality" of the reasoning of Drs. Boobis and Boisseau. The EC's rhetoric regarding the responses of these experts is inappropriate. Rather than citing to evidence that actually supports the EC's stance on these hormones in an attempt to discount the experts' advice, the EC instead seeks to impugn the credibility of the impartial individuals who have agreed to assist the Panel in its endeavors. Rather than a negative, the United States views the fact that Drs. Boisseau and Boobis "have both served on a JECFA panel

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[153] *See*, *e.g.*, U.S. Rebuttal Submission, Section II.B.4; U.S. Comments on the Experts' Responses, Section C.6.

[154] *See* Dr. Boobis' review of the Daxenberger studies on MGA and misuse. Dr. Boobis Responses (Question 62), p. 51.

[155] *See*, *e.g.*, U.S. Rebuttal Submission, Section II.B.4.

that examined some of these hormones" as testament to their qualifications, as well as evidence against the EC's refrain that they lack relevant experience in the study of the hormones.

173. The EC notes that the opinions of Drs. Boobis and Boisseau are "based on the assumption that there is a dose-response relationship (threshold), despite the accumulation of so much recent evidence showing that this assumption can no longer be valid for a number of these hormones, certainly for oestradiol 17β, progesterone, testosterone and zeranol." Despite having stated as much throughout its comments, the EC again ignores that none of the experts agree with the EC's opinion:

> Estradiol 17β: Dr. Boisseau: "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."[156] Dr. Boobis: "[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity." Dr. Guttenplan: "an adverse effect cannot be ruled out, but it is unlikely if good veterinary practices are followed." 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."[157]
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> Testosterone and progesterone: Dr. Boisseau (regarding both hormones): "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of [either hormone] are related to a mechanism other than hormonal activity."[158] Dr. Guttenplan: "Progesterone, testosterone have been extensively investigated and the assessment seems sound and is based on the no effect level and a safety factor. (JECFA meeting 52, report-WHA TRS 893)." Dr. Boobis: "[t]here is no evidence that the hormones testosterone or progesterone have genotoxic potential."[159]
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> Zeranol: Dr. Boisseau: "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of zeranol are related to a mechanism other than hormonal activity."[160] Dr. Guttenplan: "[t]here is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β [*i.e.*, including zeranol], when consumed as residues in meat have genotoxic potential."[161] Dr. Boobis: "[t]here is no convincing evidence that trenbolone acetate, MGA and zeranol are

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[156] Dr. Boisseau Responses (Question 16), p. 12.

[157] Dr. Cogliano Responses (Question 18), p. 1.

[158] Dr. Boisseau Responses (Question 21), p. 16.

[159] Dr. Boobis Responses (Question 21), p. 24.

[160] Dr. Boisseau Responses (Question 21), p. 16.

[161] Dr. Guttenplan Responses (Question 21), p. 6.

> genotoxic. They were negative in a range of tests for genotoxicity. . . [t]hus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo."[162]

174. The EC complains that Drs. Boobis and Boisseau reached their conclusions despite the fact that "available evidence is insufficient or there are total gaps in our knowledge." Again, the EC presents no evidence in support of this conclusion, and it is a statement with which the experts do not agree.[163]

175. The EC invokes Drs. Sippell, De Brabander and Cogliano, and notes that although "they have not expressed themselves on this precise question" the EC is sure that, had they responded, they would have supported the EC's argument. This is simply conjecture, and it contradicts the EC's earlier objection to experts responding to questions which they had not previously indicated themselves capable of answering.[164]

176. Question 62: The EC refers to its comments on the responses of Drs. Boisseau and Boobis from the previous question. The United States does the same. The EC insinuates its opinion for that of Dr. Boisseau, noting that Dr. Boisseau's statement only makes sense if it "was to be understood that the gaps and uncertainties identified by the EC in its risk assessment are such as to require further research and investigation." The United States finds Dr. Boisseau's response to be sufficiently clear without the EC's additional assistance: "these new data do not demonstrate any important gaps, insufficiencies and contradictions in the scientific information used by JECFA for conducting its risk assessments."

177. The EC complains of Dr. Boobis' lack of "any specific expertise" and claims to have clarified Dr. Boobis' responses on the basis of " a more careful examination by a real expert." The EC's rhetoric is inappropriate and misplaced. The purpose of this exercise is not to have the EC rewrite the responses of the experts whose assistance the Panel has solicited with the opinions of "real experts" assisting the EC in arguing this dispute. This would defeat the entire purpose of the Panel's seeking advice from an impartial group of experts in order to make sense of the technical arguments raised by the parties. The United States has provided a detailed argument of why the Leffers study reviewed by the EC's "expert" does not stand for the

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[162] Dr. Boobis Responses (Question 21), p. 24.

[163] *See* U.S. Comments on the Experts' Responses, Section C.3(c).

[164] *See* EC's Comments on the Experts' Responses (Question 2) ("Dr. Boisseau's reply that 'In my e-mail of 26/04/06, I have indicated that I did not think that I am in the position to reply to this question' calls into question the reliability of his answer to question no 1 and indeed to the other questions.)

proposition the EC contends it does.[165] Dr. Boobis concludes the following regarding alleged gaps in the scientific information:

> There is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat from treated animals can be assessed. Whilst additional information has been obtained on a number of aspects of the hormones in question, this was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded on previous knowledge. The evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion.

178. The EC agrees with Dr. Guttenplan, who it contends "provides some examples of the areas in which gaps and uncertainties have been identified and indicates some of the additional research that is required before the EC would be able to conduct a more complete risk assessment." The EC's endorsement of Dr. Guttenplan's response is ironic since the majority of the purported gaps identified in his response relate to estradiol 17β, the hormone for which the EC claims to have conducted a risk assessment within the meaning of Article 5.1 of the SPS Agreement.[166] If, as the EC appears to contend in its comments, there are substantial gaps in this data, it is unclear how the EC can justify a permanent ban on its use. The United States notes the following comments from Dr. Guttenplan regarding the provisionally banned hormones, for which the EC claims substantial gaps in the scientific data:

> Question 21: "There is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential. There is some evidence that certain of the hormones have genotoxic potential, but generally the potential is weak. Testosterone and progesterone are negative in genotoxic assays. Zeranol can induce transformation of breast epithelial cells in culture with efficiency similar to that of estradiol, but the mechanism is not known, and it is negative or marginally active in other assays. Trenbolone is either negative or marginally active in in vitro genotoxic assays. MGA is negative in genotoxicity assays. Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice."
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> Question 61: "Progesterone, testosterone have been extensively investigated and the assessment seems sound and is based on the no effect level and a safety factor. (JECFA meeting 52, report-WHA TRS 893)." "Melengestrol acetate. The assessment for

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[165] *See* U.S. Comments on the Experts' Responses, paras. 79-80.

[166] *See* EC First Written Submission, para. 17.

melengestrol acetate seems sound. Thorough metabolic and estrogenic studies have been carried out. Actual levels in beef were not provided. (JECFA 62 FNP 41/16)."[167]

D. Conclusion

179. The EC's comments on the experts' responses fail to provide any evidence or argument that discounts the experts' advice to the Panel. As demonstrated by the United States in its June 30, 2006 filing on the experts' responses and the U.S. comments above, the experts' responses confirm that the EC has failed to base its permanent ban on meat and meat products from cattle treated with estradiol 17β for growth promotion purposes on a risk assessment within the meaning of Article 5.1 of the SPS Agreement because, *inter alia*, the EC has failed to conduct a "risk assessment, as appropriate to the circumstances" and has failed to support the scientific conclusions set out in its Opinions with the scientific evidence cited therein. In addition, the EC's bans on meat and meat products from cattle treated with any of the other five hormones are not provisional measures within the meaning of Article 5.7 of the SPS Agreement because they are not based on "available pertinent information" nor is there insufficient scientific evidence to conduct a risk assessment for each of the hormones.

[167] *See* U.S. Comments on the Experts' Responses, para. 48 for a discussion of Dr. Guttenplan's comments on trenbolone.