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

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

June 30, 2006

A. Introduction

1. The United States appreciates this opportunity to provide comments on the responses received from the six scientific experts and the three international organizations selected by the Panel. The United States will first provide a context for the experts' and organizations' responses in light of the proper role of scientific experts in this dispute, and then provide comments on the responses and suggestions for clarifications that may make the responses more useful in the context of the present dispute. Finally, the United States will provide a summary of the conclusions that may be drawn from the experts' responses.

B. The role of scientific experts

2. As previously noted by the United States in its November 3, 2005 comments on the Panel's proposed working procedures for consultation with the experts, the role of scientific experts is a narrow one. Scientific experts may provide a panel information, advice, and their opinions on certain aspects of the matter that is the subject of the dispute.[1] Experts can provide a panel with vital perspectives, information, and advice on technical and scientific issues, affording a panel the ability to make legal determinations such as whether a measure is indeed based on a risk assessment or satisfies the conditions for a provisional measure within the meaning of the WTO *Agreement on the Application of Sanitary and Phytosanitary Measures* ("SPS Agreement").

C. Comments on the experts' responses

3. The Panel's questions to the experts and international organizations expressed several themes. While, not surprisingly, the experts have not provided identical responses to each question, they are in agreement on several key propositions.

4. The United States has observed the following themes in the Panel's questions:

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[1] *See Agreement on the Applications of Sanitary and Phytosanitary Measures*, Article 11.2; *Understanding on Rules and Procedures Governing the Settlement of Disputes*, Article 13.

(1) Risk assessment:[2] What international guidance materials exist for conducting a risk assessment for veterinary drug residues? What are the necessary steps for a risk assessment? Do the European Communities' ("EC's") Opinions[3] satisfy the necessary steps comprising a risk assessment?

(2) Scientific evidence relating to estradiol 17β:[4] Does the scientific evidence cited in the EC's Opinions demonstrate that carcinogenic effects of estradiol 17β are related to a mechanism other than hormonal activity? Does the scientific evidence demonstrate that estradiol 17β, when consumed as a residue in meat, is genotoxic? Does the scientific evidence demonstrate that estradiol 17β will have carcinogenic or tumorigenic effects at levels found in residues in meat from treated cattle?

(3) Scientific evidence relating to the five provisionally banned hormones:[5] Is the scientific evidence and information relating to the five hormones sufficient to conduct an assessment of the risks to human health from consumption of meat from cattle treated with the five hormones for growth promotion purposes? Does the scientific evidence cited by the EC in its Opinions demonstrate that any of the five hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity? Do the scientific materials produced and cited by the EC (including the "17 Studies"[6]) identify any gaps or insufficiencies in the scientific evidence such that more study is necessary before the risk from consumption of meat from cattle treated with the five hormones for growth promotion purposes can be assessed?

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[2] *See*, *e.g.*, Panel's Questions to the Experts, Questions 3-14.; 36-37; 55; 57.

[3] The EC's Opinions, or "risk assessments", are comprised of the "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") (Exhibit US-4); the Review of Specific Documents Relating to the SCVPH Opinion of 30 April 99 on the Potential Risks to Human Health from Hormone Residues in Bovine Meat and Meat Products, dated May 3, 2000 ("2000 Review") (Exhibit US-17); and the "Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health on Review of previous SCVPH opinions of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products", 10 April 2002 ("2002 Opinion") (Exhibit US-1).

[4] *See*, *e.g.*, Panel's Questions to the Experts, Questions 13-20.

[5] *See*, *e.g.*, Panel's Questions to the Experts, Questions 21; 25; 38-42; 61-62.

[6] The EC commissioned several (17) studies in 1998-1999 (collectively the "17 Studies"), ostensibly to fill data gaps and develop support for the conclusions set out in the Opinions. *See* U.S. First Written Submission, para. 24; EC First Written Submission, para. 142.

(4) Scientific evidence relating to the hormones generally:[7] Has each of the hormones used for growth promotion purposes in cattle been evaluated for a sufficient period with no evidence of adverse effects to adequately address any concern regarding long latency periods of cancer? Do epidemiological studies cited by the EC identify a link between cancer and residues of the hormones in meat? Do materials cited by the EC demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations? Do materials cited by the EC demonstrate other human health risks from consumption of residues of the hormones in meat from cattle treated for growth promotion purposes, such as effects on the immune system?

(5) Scientific evidence relating to residues:[8] To what extent did the EC evaluate evidence on the actual residue levels of natural and synthetic hormones? Did the EC take these levels into account in its Opinions? Why, and how did the Joint FAO/WHO Expert Committee on Food Additives ("JECFA") re-evaluate the three natural hormones in 1999?

(6) Scientific evidence relating to good veterinary practices:[9] Do materials cited by the EC demonstrate that there is a risk to human health from the misuse of growth promoting hormones in the United States? Has the EC assessed this risk? Do materials cited the EC regarding misuse or abuse of the hormones call into question Codex Alimentarius Commission ("Codex") standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes?

5. These themes relate to Annex A, paragraph 4 (defining risk assessment) and to Article 5 of the SPS Agreement, most notably Article 5.1 (whether the EC's ban on estradiol 17β is based on a risk assessment, as appropriate to the circumstances); Article 5.2 (whether the EC's purported risk assessment takes into account available scientific evidence; relevant processes and production methods; relevant inspection, sampling and testing methods); Article 5.6 (whether the EC's import ban on meat and meat products is not more trade-restrictive than required to achieve its appropriate level of sanitary protection); and Article 5.7 (most notably, the first two elements of Article 5.7's four-part cumulative test: whether the EC's provisional bans have been imposed in a case where relevant scientific evidence is insufficient and whether they have been adopted on the basis of available pertinent information).

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[7] *See*, *e.g.*, Panel's Questions to the Experts, Questions 22-24; 26; 43; 52-54; 59-60.

[8] *See*, *e.g.*, Panel's Questions to the Experts, Questions 27-35.

[9] *See*, *e.g.*, Panel's Questions to the Experts, Questions 44-51.

6. In addition, these themes are set against the following factual backdrop, described in greater detail in the U.S. first written submission.[10] The EC's hormone ban prohibits the importation and marketing of meat and meat products from cattle to which any of the six hormones (estradiol 17β; testosterone; progesterone; zeranol; trenbolone acetate; and melengestrol acetate) have been administered for growth promotion purposes. The United States permits the administration of these hormones to cattle for that very purpose. Five of the six hormones (estradiol 17β, progesterone, testosterone, zeranol, and trenbolone acetate) are administered to cattle as subcutaneous implants in the animals' ears. The ears are then discarded at slaughter and do not enter the human food supply. The sixth hormone, melengestrol acetate, a synthetic progestogen, is administered as a feed additive.

7. Three of the six hormones at issue in this proceeding (estradiol 17β; progesterone; and testosterone) are naturally occurring, "endogenous" hormones produced by both humans and animals used for human food. Each of these hormones is produced throughout the lifetime of every man, woman and child, and is required for normal physiological functioning and maturation. With respect to chemical structure, the natural hormones used for growth promotion purposes in cattle are identical to the estradiol 17β, progesterone and testosterone naturally produced in the human body. Furthermore, when administered exogenously, each of these hormones enters the same metabolic pathway as the endogenously produced hormone and its metabolites are indistinguishable from those that are produced naturally. Endogenous production of estradiol 17β, progesterone and testosterone in humans is orders of magnitude higher than the relatively small amounts of these hormones ingested from residues in meat.

8. The other three hormones (zeranol; trenbolone acetate; and melengestrol acetate) are synthetic hormones that mimic the biological activity of the natural hormones. Trenbolone acetate mimics testosterone, zeranol mimics estradiol 17β, and MGA mimics progesterone.

9. Codex standards exist for the use of five of the six hormones for growth promotion purposes. Upon review of risk assessments conducted by JECFA and recommendations by the Codex Committee on Residues of Veterinary Drugs in Food ("CCRVDF"), Codex[11] adopted recommended maximum residue limits ("MRLs"), where appropriate, for estradiol 17β, progesterone, testosterone, trenbolone acetate and zeranol. Codex adopted these recommended MRLs to ensure that consumption of animal tissue containing residues of these hormones do not pose a risk to consumers. JECFA recommended an acceptable daily intake ("ADI") for melengestrol acetate at its 62nd Meeting in 2004.

10. Against this background, the EC has alleged that it is now justified in permanently banning the import of meat and meat products from cattle treated with estradiol 17β for growth

[10] *See* U.S. First Written Submission, Sections III.B and III.C (pages 10-25).

[11] Codex is recognized as specified as the relevant international standards-setting body in the SPS Agreement. *See* SPS Agreement, paragraph 3(a) to Annex A.

promotion purposes, and provisionally banning the import of meat and meat products from cattle treated with the five other hormones for growth promotion purposes. The EC alleges to have based its ban on estradiol 17β on a "risk assessment" within the meaning of Article 5.1 and paragraph 4 of Annex A of the SPS Agreement, and to have implemented a provisional ban for the five remaining hormones within the meaning of Article 5.7 of the SPS Agreement because, unlike JECFA, it was unable to complete a risk assessment for any of the hormones.[12] While at the same time banning meat from cattle treated with any of the six hormones for growth promotion purposes, the EC permits the administration of hormones to farm animals for certain therapeutic and zootechnical purposes, and the eventual marketing of meat from these animals.

(1) Risk assessment

11. The question of what constitutes a risk assessment is relevant to the obligation in Article 5.1 of the SPS Agreement in that Members must base their measures on a risk assessment as defined in Annex A, paragraph 4 of the SPS Agreement. The responses from the experts confirm that there is a certain internationally-recognized form that risk assessments should take and that there is consensus among the experts that the EC's purported risk assessment for estradiol 17β fails to satisfy the necessary elements comprising such an assessment.

(a) *Risk assessment procedures generally*

12. The experts' responses confirm several points relating to risk assessment procedures, namely that: (1) a wealth of international guidance exists for the conduct of a risk assessment of veterinary drug residues; (2) both quantitative and qualitative risk assessments should satisfy the four steps for a risk assessment (hazard identification; hazard characterization; exposure assessment; and risk characterization); (3) risk assessments, including those conducted by JECFA on the six hormones, have not been limited by a "deterministic approach"[13]; and (4) JECFA requires a complete database in order to recommend an acceptable daily intake ("ADI") unless it can adopt default assumptions that would lead to a more conservative risk assessment.

13. As noted by Codex, JECFA and Dr. Boobis, there are numerous international documents and guidance materials relevant to the assessment of veterinary drugs in food, dating back to at

[12] *See*, *e.g.*, EC First Written Submission, para. 17. (Noting that its ban, Directive 2003/74/EC, is "based on a comprehensive risk assessment and, thus, is fully compliant with the DSB recommendations and rulings. In particular, as stipulated by the Appellate Body, the results of the risk assessment 'sufficiently warrant' the definite import prohibition regarding one of the hormones (Article 5.1 of the SPS Agreement), and provide the 'available pertinent information' on the basis of which the provisional prohibition regarding the other five hormones has been enacted (Article 5.7 of the SPS Agreement).")

[13] A "deterministic approach" to risk assessment means simple, point (single-value) estimates of risk. "Deterministic" risk assessment does not account for uncertainty and variability in the parameters of the risk assessment including exposures, dose-response and normal variation in the exposed populations, and typically calls for highly conservative, worst-case assumptions in exposure, dose and sensitive populations. *See*, *e.g.*, Hattis and Burmaster, Risk Analysis 14(5): 713-730 (1994).

least 1987.[14] In addition, Dr. Boisseau comments that the assessment of such drugs has been "internationally harmonised through scientific conferences and it is possible to say there is an international non written agreement on this rationale."[15] As noted by JECFA, "[a]ll of these documents are the outcome of international expert meetings and represent the agreed views of the participating experts and several of those have also been published in the scientific literature."[16] Although there are no Codex standards *per se* on the conduct of a risk assessment (such guidance is currently in draft form[17]), as noted by JECFA, "[t]he elaboration and application of risk assessment principles are within the responsibility of the scientific expert bodies [*i.e.*, JECFA]."[18]

14. In terms of the components comprising a risk assessment, the experts' responses confirm that there are four essential elements: (1) hazard identification; (2) hazard characterization; (3) exposure assessment; and (4) risk characterization.[19] The one caveat to this rule is provided by Dr. Vincent Cogliano, who notes that, for purposes of hazard characterization, "[a] qualitative risk assessment can consider the presence or absence of dose-response relationships."[20] JECFA's response takes this thought a step further, noting that a dose-response assessment is an integral part of hazard characterization, and can be "done in a quantitative or a qualitative way. In the qualitative sense this is the determination of a no-effect level from an experimental or epidemiological study. For the hormones JECFA used this approach."[21] The definition of "hazard characterization" provided by Codex confirms that a dose-response assessment is

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[14] *See* 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; Responses to Questions from the Panel of Dr. Alan Boobis ("Dr. Boobis Responses") (Question 3), pp. 10-11.

[15] Responses to Questions from the Panel of Dr. Jacques Boisseau ("Dr. Boisseau Responses") (Question 4), p. 2. Indeed, as noted by the United States in its first written submission, the EC acknowledges that there is a general form which a risk assessment must take. *See* U.S. First Written Submission, para. 139, *citing* EC 1999 Opinion, p. 70 ("Executive Summary") (Exhibit US-4).

[16] JECFA Responses (Question 3), p. 3.

[17] *See* Codex Responses (Question 4), p. 5; Dr. Boobis Responses (Question 3), p. 11.

[18] JECFA Responses (Question 3), p. 2.

[19] JECFA Responses (Question 6), p. 3; Codex Responses (Question 6), p. 6; Dr. Boobis Responses (Question 6), p. 13; Dr. Boisseau Responses (Question 6), pp. 4-5; Responses to Questions from the Panel of Dr. Joseph Guttenplan ("Dr. Guttenplan Responses") (Question 6), p. 2.

[20] Responses to Questions from the Panel of Dr. Vincent Cogliano ("Dr. Cogliano Responses") (Question 11), p. 1.

[21] JECFA Responses (Question 8), p. 4.

integral to this step of risk assessment.[22] The EC's Opinions fail to engage in any such evaluation because they rely instead on the conclusion that estradiol 17β is genotoxic; however, as discussed in greater detail below, and as confirmed by the scientific experts, the EC fails to adduce evidence of genotoxic or carcinogenic effects at levels below those associated with a hormonal response.

15. Finally, the experts' responses clarify two key aspects of JECFA's risk assessment procedure, namely that JECFA's assessments of the six hormones are not limited by a "deterministic approach" and that JECFA requires a complete database in order to complete a risk assessment and set an ADI (as it has done for the hormones at issue) unless it can adopt default assumptions that would lead to a more conservative risk assessment.[23] As to the former point, Dr. Boisseau notes that, rather than taking a "deterministic" approach, "JECFA was perfectly aware about this kind of non linear situation[s]," and that, "[i]f, in 1999, the 52nd JECFA recognized that oestradiol-17β 'has a genotoxic potential', it concluded nevertheless that 'the carcinogenicity of oestradiol-17β was probably a result of its interaction with hormone receptors'. Therefore it did not take into consideration a non linear situation in its risk assessment."[24]

16. Dr. Boobis reiterates this point, noting that the results of JECFA's risk assessment are based on scientific evidence as opposed to a predetermined result, "JECFA['s] risk assessment concluded that the dose-response relationship for all of the endpoints was non-linear and that there was a threshold dose below which there was no appreciable risk over a lifetime of exposure. Hence, a deterministic approach, via the establishment of ADIs, was appropriate according to the procedures followed by the Committee."[25] Finally, as noted by JECFA itself, "JECFA's assessment process is based on the mechanism of action of the compound to be evaluated, non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect. In such a case, as for the hormones, a no-effect level can be determined."[26]

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[22] Codex Responses (Question 6), p. 6 ("**Hazard characterization.** The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.") (Emphasis added). *See* JECFA Responses (Question 6), p. 3 (hazard characterization "includes dose-response assessment, considerations on species sensitivity, relevance of specific effect for humans etc.")

[23] *See* Dr. Boobis Responses (Question 9), p. 15.

[24] Dr. Boisseau Responses (Question 7), p. 6.

[25] Dr. Boobis Responses (Question 7), p. 13.

[26] JECFA Responses (Question 7), p. 4.

17. As to the latter point, Drs. Boisseau and Boobis, and JECFA confirm that JECFA only allocates a final ADI for a veterinary drug if the scientific database is complete and there are no outstanding scientific issues. As noted by JECFA, "[i]f there are substantial gaps and important information missing, JECFA can not establish an ADI."[27] The only alternative to this rule is a situation where JECFA can "adopt default assumptions that would if anything lead to a more conservative risk assessment than would be the case otherwise."[28] JECFA has set final ADIs for each of the hormones in this dispute, indicating that from its point of view, the scientific database on the hormones was complete and void of substantial gaps. As noted by Dr. Boisseau, "[f]or the hormonal growth promoters, JECFA has considered that, given the quality and the quantity of the data, it was possible to carry out a complete quantitative risk assessment."[29]

(b) *The EC has failed to complete a "risk assessment" for estradiol 17β*[30]

18. The experts' responses confirm that the EC has not completed a risk assessment for estradiol 17β. When prompted to examine the EC's Opinions in light of the four steps of risk assessment discussed above, the experts expose numerous weaknesses in the EC's purported risk assessments and elaborate on the EC's failure to complete the necessary steps as well as assess critical factors such as the bioavailability of estradiol 17β and human DNA repair mechanisms.

19. The experts' responses confirm that, while the EC Opinions engage in hazard identification,[31] the first step of a risk assessment, the Opinions fail to complete any of the remaining three components (hazard characterization; exposure assessment; and risk characterization). Dr. Boobis notes, "[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. There was little in the way of hazard characterization, and no independent exposure assessment was undertaken,"[32]

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[27] JECFA Responses (Question 11), p. 10.

[28] Dr. Boobis Responses (Question 9), p. 15; *see* Dr. Boisseau Responses (Question 9), p. 7 ("The Canadian statement stipulating that 'it is recognized that JECFA only allocates an ADI for a food additive or a veterinary drug under review when JECFA considers that its scientific data base is complete and that there is no outstanding scientific issue' is correct."); JECFA Responses (Question 11), p. 10.

[29] Dr. Boisseau Responses (Question 12), p. 8.

[30] This Section of the Submission focuses on whether or not the EC has adhered to the relevant steps for conducting a risk assessment. A discussion of whether or not the scientific conclusions relating to estradiol 17β drawn by the EC are actually supported by the scientific evidence is presented in Sections C(2), C(4) and C(5)-C(6) below.

[31] *See* U.S. First Written Submission, para. 140 ("There is no great challenge to completing this first-step in a hormone risk assessment – the potential biological effects of hormones, some of which are adverse, are generally not in dispute in the scientific community.")

[32] Dr. Boobis Responses (Question 13), p. 17.

indicating that the EC's Opinions "do[ ] 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."[33] In other words, "[t]here was no attempt to estimate the potential occurrence of adverse effects in humans following exposure to levels of hormones found in meat from treated animals."[34]

20. Dr. Joseph Guttenplan agrees that the EC has satisfied the first element of a risk assessment (hazard identification) by "identifying the potential for adverse effects on human health of oestradiol-17β."[35] Yet, like Dr. Boobis, Dr. Guttenplan opines that the EC's Opinions "taken together, ha[ve] a mixed rating in following the Codex guidelines,"[36] noting that "[t]he hazard characterization is more limited since there is only one animal model that is well characterized and this is in the hamster kidney. As kidney is not a known target of estradiol in humans the extrapolation to humans is uncertain. The risk characterization is very qualitative at best."[37] Dr. Boobis comments that the EC appears to have stopped prematurely (at the hazard identification stage) in its assessment of estradiol 17β "based on the results of a small number of non-standard tests of genotoxicity, with equivocal weak responses. It is not clear if the EC applied a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking into account the totality of the available data, as was the case with JECFA."[38] As a result, the EC's Opinions make little progress beyond the first step of risk assessment, hazard identification.

21. The experts' responses confirm that the EC's Opinions fail to engage in a dose-response assessment, which is part of the hazard characterization stage (the second step of risk assessment). Such an assessment would have been appropriate in the analysis of a hormone such as estradiol 17β for which a wealth of scientific evidence exists indicating that any effects caused by estradiol 17β are through the receptor-mediated (endocrine), cell division stimulating activity of the hormone, and not by genotoxic (non-endocrine) effects. Rather than evaluating this evidence in its Opinions, the EC relies instead on its assertion that estradiol 17β is genotoxic

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[33] Dr. Boobis Responses (Question 14), p. 18. Regarding the notion that residue levels found in meat from treated cattle cause genotoxic effects, Dr. Boisseau opines "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." Dr. Boisseau Responses (Question 13), p. 11.

[34] Dr. Boobis Responses (Question 13), p. 18.

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

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

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

[38] Dr. Boobis Responses (Question 12), p. 17.

as an excuse for failing to conduct a dose-response assessment.[39] As noted by Dr. Boobis, it was improper for the EC to stop its assessment of estradiol 17β at this stage, "[f]or compounds that are known or assumed to be genotoxic via DNA reactivity, genotoxic potential would normally have to be confirmed in vivo before this endpoint would be used as the basis for a risk assessment."[40] As discussed in greater detail below, and as confirmed by the experts, the scientific studies cited by the EC fail to demonstrate this potential in vivo.[41]

22. The experts' responses also confirm that the EC has failed to conduct a proper exposure assessment for estradiol 17β, the third step of risk assessment. The EC describes what it views as the necessary elements of a proper exposure assessment as follows:

> for the purposes of exposure assessment from the residues of these hormones, it is not so much necessary to compare (if it were only possible!) the two situations and then try to quantify how much one is more risky than the other and to what measurable level the risk is likely to occur, but rather to assess a situation of additive risks arising from the cumulative exposures of human to multiple hazards, in addition to the endogenous production of some of these hormones by the animals and the human beings.[42]

The Panel accordingly asked the experts whether or not the EC has accomplished this goal by assessing these "additive risks," thereby completing the exposure assessment step of its purported risk assessment. The experts agree that the EC has not.

23. Dr. Boisseau comments, "[t]he European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute [to such a risk]."[43] Dr. Boobis notes, "[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 multiple hazards." Finally, Dr. Guttenplan opines, "[i]n general the EC do not attempt to evaluate 'the additive risks arising from the cumulative exposures of humans to multiple hazards,

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[39] *See* Dr. Boobis Responses (Question 13), pp. 17-18.

[40] Dr. Boobis Responses (Question 36), p. 36, citing CVMP (2004). Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing; *see* Dr. Boisseau Responses (Question 36), p. 20 ("A dose-response assessment is not feasible for substances that are found to be genotoxic if . . . this genotoxic potential can be expressed in in vivo conditions.")

[41] *See* Dr. Boobis Responses (Questions 16, 18, 20 and 52), pp. 19-20, 22, 23, and 44 (concluding that estradiol 17β is not genotoxic in vivo); Dr. Boisseau Responses (Question 13), pp. 9-11; *see* Section C(2)(b) below.

[42] EC Answers to Panel Questions, para. 151.

[43] Dr. Boisseau Responses (Question 55), p. 26.

in addition to the endogenous production of some of these hormones by animals and human beings'."[44]

24. For example, the experts' responses confirm that the EC's Opinions fail to take into account treatments of cattle with hormones for purposes other than growth promotion, such as therapeutic or zootechnical administration of the hormones. As noted by Dr. Boisseau:

> [a]s soon as the [EC] accepts to consider[ ] these residues resulting from these therapeutic and zootechnical use[s] of oestradiol-17β as negligible [*i.e.*, by permitting their ongoing use for these purposes], it enters into a quantitative, or at least in a semi quantitative, exposure assessment procedure for these [ ] 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.[45]

Dr. Boobis comments, "[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."[46] Dr. Guttenplan indicates that the EC's decision to except zootechnical or therapeutic treatments from its ban is "a reasonable response," yet he does not appear to address the Panel's inquiry, *i.e.*, whether the EC, in its Opinions, took these treatments into account in an assessment of cumulative effects.[47]

25. In defense of its lack of an exposure assessment, the EC has argued that "the only rationale that can be inferred from the available data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be."[48] The experts' responses confirm that this is "indeed a very weak statement by the EC."[49] Dr. Boisseau reiterates his comment that the EC has simply failed to "assess quantitatively the extent to which residues of growth promoting

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[44] Dr. Guttenplan Responses (Question 55), p. 11. Note that Dr. Guttenplan's response appears to conflict with his earlier opinion that the EC had completed an exposure assessment. It is unclear how the EC could have in fact completed an exposure assessment where, as confirmed by Dr. Guttenplan in his response to Question 55, it has failed to engage in the necessary analysis.

[45] Dr. Boisseau Responses (Question 57), p. 27. *See also* Dr. Boisseau Responses (Question 58), p. 26 ("The European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute to 'additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'.")

[46] Dr. Boobis Responses (Question 57), p. 47.

[47] Dr. Guttenplan Responses (Question 57), p. 12.

[48] EC Answers to Panel Questions, para. 94.

[49] Dr. Guttenplan Responses (Question 58), p. 12.

hormones in meat contribute to 'additive risks'."[50] Dr. Boobis concurs, and notes that "[w]ithin quite broad limits, higher exposure would not result in any increase in risk."[51]

26. The EC's failure to conduct an exposure assessment is all the more stark in light of JECFA's completion of just such an assessment for estradiol 17β. As noted by 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 . . . there was no risk for consumers' health associated with the estimated ingestion of these residues."[52] Dr. Boobis agrees that the additive, or aggregate risk was assessed by JECFA, and that exposures from residues in meat from cattle treated with the natural hormones for growth promotion purposes "were considered to represent a trivial increase in overall exposure to hormonally-active material from other exogenous sources and in particular from endogenous sources."[53]

27. In addition to failing to complete the four steps for a risk assessment, the EC's Opinions also fail to properly address critical factors such as the bioavailability of estradiol 17β[54] and DNA repair mechanisms.[55] The experts' responses note that bioavailability relates to the oral route of exposure to hormone residues, a route that is "not the most efficient,"[56] and that the bioavailability of a substance, in this case estradiol 17β, "has to be taken into consideration in the risk assessment, in particular at the third step regarding the exposure assessment of residues."[57] Indeed, as a general rule "only that fraction of the dose that is bioavailable is toxicologically relevant."[58] The United States has argued that the EC has failed to take into

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[50] Dr. Boisseau Responses (Question 55), p. 26.

[51] Dr. Boobis Responses (Question 58), p. 48. Dr. Boobis notes that "The EC Opinions and other materials referred to by the EC do not quantify the extent to which residues of the hormones contribute to aggregate exposures or cumulative exposures to multiple hazards." Dr. Boobis Responses (Question 55), p. 45.

[52] Dr. Boisseau Responses (Question 56), p. 26.

[53] Dr. Boobis Responses (Question 56), p. 46.

[54] Note that the EC has also failed to take bioavailability into account for the five provisionally-banned hormones. A discussion of biovailability is perhaps most pertinent, however, to a discussion of estradiol 17β, for which the EC claims to have completed a risk assessment.

[55] Bioavailability and DNA repair mechanisms should have been addressed in the EC's exposure assessment, had it completed one.

[56] Dr. Boisseau Responses (Question 43), p. 22.

[57] Dr. Boisseau Responses (Question 43), p. 23.

[58] Dr. Boobis Responses (Question 43), p. 40. *See* Dr. Guttenplan Responses (Question 43), p. 10 ("only the bioavailable chemical can produce adverse (or any) effects, thus in terms of risk assessment, only the portion of the dose of chemical that is bioavailable is significant.")

account the low bioavailability of estradiol 17β in its assessment of that hormone, and none of the experts' responses appear to indicate otherwise.[59]

28. The experts agree that estradiol 17β has low oral bioavailability. Indeed, Dr. Boisseau notes that "oestradiol 17-β is inactive orally,"[60] and Dr. Boobis states that "exposure [to estradiol] is via the oral route, and bioavailability by this route is very low (< 5%)."[61] In contrast, Dr. Guttenplan opines that the bioavailability of "estrogen" is "low but not insignificant."[62] However, Dr. Guttenplan's reply: (1) relies on materials cited by the EC that do not in fact demonstrate a higher bioavailability for estradiol 17β than previously thought; and (2) miscasts as "paradoxical" a U.S. argument relating to bioavailability.

29. The materials cited by the EC in its Opinions and by Dr. Guttenplan in his responses do not demonstrate a higher bioavailability for estradiol 17β than previously thought. In support of his statement that bioavailability is higher than previously thought, Dr. Guttenplan cites directly to the EC Rebuttal Submission and its statement that "[m]etabolic studies of orally administered 17β-oestradiol indicate that as much as 20 percent of a 2 mg dose of micronized E2 is absorbed, with a serum half-life in the range of 2 to 16 hours (Zimmermann et al., 1998; Vree and Timmer, 1988; Ginsburg et al., 1998)."[63] However, upon review of these studies, it is clear that none of these references contains data that allow estimation of bioavailability. Rather all of the studies were conducted with an entirely different objective, the demonstration of bioequivalence. As a result, they do not stand for the conclusion for which they have been cited by the EC and Dr. Guttenplan.

30. Dr. Guttenplan indicates that a conclusion reached by the United States (that bioavailability of estradiol 17β is low)[64] based in part on a EC study evaluating the metabolism

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[59] *See* U.S. First Written Submission, paras. 146, 88-89.

[60] Dr. Boisseau Responses (Question 43), p. 23. Dr. Boisseau notes that the "[n]atural hormones are known to be poorly bioavailable in humans," and that the bioavailability of the synthetic hormones "ha[s] not been determined." Therefore, in a risk assessment of those hormones, as was the case in the JECFA assessment, "all their residues have been considered as being totally bioavailable." Dr. Boisseau Responses (Question 43), p. 23. *See* Dr. Boobis Responses (Question 43), p. 40.

[61] Dr. Boobis Responses (Question 40), p. 39.

[62] Dr. Guttenplan Responses (Question 43), p. 10. Dr. Guttenplan opines that "[i]t appears that the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%), if estrone is also taken into account."

[63] *See* Dr. Guttenplan Responses (Question 43), p. 11.

[64] *See* U.S. Rebuttal Submission, para. 41. Note that the study's author confirms the U.S. argument regarding bioavailability of estradiol 17β, concluding that the study's result "indicates that 17β-estradiol is not absorbed intact in the human intestinal tract." Hoogenboom, Investigations on the metabolism of 17β-estradiol by bovine hepatocytes, human intestinal and breast cells, and the genotoxic and estrogenic properties of the metabolites

of estradiol 17β is "paradoxical" to the results of the study because, according to Dr. Guttenplan, in the study "estradiol was converted to estrone, so it must have entered the cell."[65] It is true that estradiol was converted to estrone in the study; however, the focus of the U.S. argument was the evaluation of whether or not estradiol 17β, the alleged "bad actor" implicated by the EC as a genotoxic carcinogen was transported across the single-cell layer (used to mimic the human intestinal wall in the study). Whether or not estradiol 17β entered the cells is irrelevant to the point made by the United States. Rather than being transported across the single-cell layer, all of the estradiol 17β that entered the cells was metabolized into estrone or other metabolites, which have been shown in studies cited by the EC to be benign in terms of genotoxic carcinogenicity.[66]

31. Finally, the experts agree that the EC's Opinions also fail to take into account available scientific evidence relating to DNA repair mechanisms. Dr. Boobis states that "the evidence is against direct modification of DNA in vivo by hormones in meat from treated animals, or by their metabolites produced in vivo," in part because "[t]he DNA repair processes for this are amongst the most efficient (Arai et al, 2006; Russo et al, 2004) and even if such modification did occur, it is anticipated that no heritable change would result, because of DNA repair."[67] According to Dr. Boobis, "[t]his would be true even at levels of exposure that could arise should GVP not be followed."[68] Dr. Guttenplan notes, "[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 that "the scientific materials referred to by the [EC] for the most part doesn't address DNA repair."[69]

(c) *Conclusion*

32. The experts' responses regarding the necessary components or elements of a risk assessment and their opinions as to whether or not the EC has satisfied each of those elements confirm that the EC has not conducted a risk assessment for estradiol 17β, the one hormone for

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(unpublished), p. 5. (Exhibit EC-6 (US)).

[65] Dr. Guttenplan Responses (Question 43), p. 11.

[66] Moreover, any estrone that is absorbed in the intestine will be rapidly transported to liver where it will undergo extensive first-pass metabolism, thus minimizing any potential effects that might occur from conversion of estrone back into estradiol.

[67] Dr. Boobis Responses (Question 22), p. 25.

[68] Dr. Boobis Responses (Question 22), p. 25.

[69] Dr. Guttenplan Responses (Question 22), p. 7. Dr. Guttenplan states that "since it [DNA repair] is not likely to be different for estrogen derived damage than other types of damage it is not really relevant." This statement requires clarification, as it would appear to the United States that DNA repair of estrogen-derived damage is extremely important to an analysis of whether or not that specific form of damage is occurring, and the resulting likelihood of said damage.

which it claims to have done so.[70] Therefore, the EC has failed to base its permanent ban on meat and meat products from cattle treated with estradiol 17β on a risk assessment, as required by Article 5.1 and defined in Annex A, paragraph 4 of the SPS Agreement.

(2) Scientific evidence relating to estradiol 17β

33. The question of whether scientific evidence cited in a risk assessment supports the conclusions reached in the assessment is relevant to the obligation in Article 5.1 of the SPS Agreement that Members must base their measures on a risk assessment, as appropriate to the circumstances,[71] as well as Article 5.2's requirement that risk assessments take into account available scientific evidence. The experts' responses confirm the following points regarding the scientific evidence relating to estradiol 17β cited by the EC: (1) the scientific evidence does not support the conclusion that any carcinogenic effects of estradiol 17β are related to a mechanism other than hormonal (endocrine) activity; (2) the scientific evidence does not support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones; and (3) the scientific evidence does not demonstrate that estradiol 17β will have carcinogenic or tumorigenic effects at concentrations found in residues in meat from cattle treated with hormones for growth promotion purposes.

(a) *The scientific evidence does not support the conclusion that any carcinogenic effects of estradiol 17β are related to a mechanism other than hormonal activity*

34. The experts' responses confirm that the scientific evidence cited by the EC in its Opinions does not support the conclusion that the carcinogenic effects of estradiol 17β are related to a mechanism other than hormonal activity. Dr. Boisseau notes, "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."[72] Dr. Boobis concurs, "[t]he carcinogenic effects of oestradiol appear to be a

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[70] Note that the experts' comments as to whether the EC completed the fourth step of risk assessment (risk characterization) are contained in the discussion above. The short answer is that the EC did not complete this step. Dr. Boobis: "No adequate assessment of exposure following use according to GVP was undertaken. Hence, it was not possible to complete the risk characterization phase of the assessment." Dr. Guttenplan: "[t]he risk characterization is very qualitative at best." (Dr. Boobis Responses (Question 13), p. 17; Dr. Guttenplan Responses (Question 14), p. 4).

[71] *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 (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.")

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

consequence of its endocrine activity."[73] One expert, Dr. Guttenplan, restates the conclusions of both parties, noting that while the EC has cited materials that "indicate that a mechanism other than hormonal activity is possible," the "United States and Canada cite other reports indicating that genotoxic effects of estrogens are unlikely."[74] While this statement likely requires further clarification, the United States notes that additional responses from Dr. Guttenplan appear to indicate that he is of the opinion that any carcinogenic effects of estradiol 17β are indeed linked to hormonal activity or to levels greater than those found in residues in meat from cattle treated with hormones for growth promotion purposes. For example, Dr. Guttenplan concludes that any carcinogenic effect from estradiol 17β in meat from treated cattle "is unlikely if good veterinary practices are followed."[75]

(b) *The scientific evidence does not support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones*

35. The experts' responses confirm that the scientific evidence cited by the EC in its Opinions does not support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones. As noted by Dr. Cogliano, "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans."[76] Dr. Boobis states, "whilst there are reliable studies demonstrating the genotoxicity of oestradiol in certain in vitro tests, the evidence is against any genotoxicity in vivo. Some, if not all, of the genotoxicity observed in vitro would be expected to exhibit a threshold."[77]

36. Regarding the specific studies relied upon by the EC in reaching its conclusion that estradiol 17β is genotoxic, Dr. Boobis notes that the studies "should have been evaluated on a weight of evidence basis. Several of the studies suffered from significant limitations and there were a number of well conducted studies on a variety of endpoints that should have been included in such an evaluation."[78] Dr. Boobis provides numerous citations on the issue of

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[73] Dr. Boobis Responses (Question 16), p. 19.

[74] Dr. Guttenplan Responses (Question 16), p. 4. Rather than elaborating on how the EC's Opinions support the conclusion (*e.g.*, with scientific evidence) that the carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity, Dr. Guttenplan simply recites the Opinions' conclusion that this is so.

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

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

[77] Dr. Boobis Responses (Question 18), p. 22.

[78] Dr. Boobis Responses, p. 20. *See generally* Dr. Boobis Responses (Question 62), pp. 49-58, in which Dr. Boobis provides specific critiques of several of the 17 Studies and other scientific materials cited by the EC.

genotoxicity and estradiol that were not considered by the EC in its Opinions, all of which have been published since 2000.[79] According to Dr. Boobis' analysis of the issue, none of the available evidence demonstrates that estradiol 17β is genotoxic in vivo.[80] The importance of this statement is underscored by the fact that the EC's own Committee for Medicinal Products for Veterinary Use ("CVMP") has a published guideline for evaluating the safety of residues of veterinary drugs in human food "requiring confirmation of an in vitro positive using an appropriate in vivo assay."[81] The EC has failed to explain why their evaluation of estradiol 17β is not subject to this guideline.

37. Dr. Boisseau notes that the EC provides "no data indicating that oestradiol-17β is associated with the increase of tumours in tissues or organs which are not hormone dependent," and that, "[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."[82] This comment by Dr. Boisseau is further emphasized by Dr. Boobis, who states, "the important point here is that it is the carcinogenic effect that is of concern, not in vitro genotoxicity."[83]

38. It is unclear from Dr. Guttenplan's responses whether or not he is of the opinion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones. As such, his response appears to neither bolster nor cast any doubt on the responses of the other experts who examined the issue of genotoxicity. On the one hand, Dr. Guttenplan recognizes a genotoxic mechanism, while on the other he notes a hormonal mechanism.[84] At the same time, he disagrees with the blanket EC conclusion that "it cannot be said that there exist[s] a safe level below which intakes from residue should be considered to be safe." As to this point, Dr. Guttenplan comments that the EC's conclusion is "not necessarily true," and that "for any toxin, the dose determines the risk."[85] Further, as noted above, Dr. Guttenplan has expressed the opinion that any carcinogenic effect from estradiol 17β in meat from treated cattle "is unlikely if good veterinary practices are followed,"[86] a conclusion from which one can infer that levels of estradiol 17β residue in meat from treated cattle are safe for consumers.

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[79] *See* Dr. Boobis Response (Question 16), pp. 19-20.

[80] *See* Dr. Boobis Response (Question 16), p. 19.

[81] Dr. Boobis Response (Question 16), p. 19.

[82] Dr. Boisseau Responses (Question 13), p. 11.

[83] Dr. Boobis Responses (Question 19), p. 22.

[84] Dr. Guttenplan Responses (Question 19), p. 5.

[85] Dr. Guttenplan Responses (Question 19), p. 5.

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

39. The fact that the scientific evidence cited by the EC in its Opinions fails to support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones is critical to the EC's corresponding conclusion that no threshold cannot be identified for the residues of the hormone and that there is no "safe level below which intakes from residue should be considered to be safe."[87] The experts' responses confirm that the EC has failed to adduce the necessary scientific evidence to support this conclusion. As noted by Dr. Boisseau, "[t]he scientific evidence referred to by the European Communities does not demonstrate that this statement can also apply in the case of oestradiol-17β, . . . as [this] [ ] natural hormone[ ] [is] produced by both humans and food producing animals. Therefore, even in the absence of any consumption of food coming from animals treated by growth promoting hormones, humans are naturally and continuously exposed to these natural hormones."[88]

40. Dr. Boobis agrees, stating, "[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."[89] Dr. Cogliano concurs, noting that the EC's statement regarding the lack of a threshold has not been demonstrated by the scientific evidence.[90] Dr. Cogliano also opines that the U.S. stance on thresholds has not been supported by the scientific evidence, but this opinion does not appear to be relevant to the evaluation at hand, which is whether or not the EC, in banning the import of meat from cattle treated with estradiol 17β for growth promotion purposes, adduces the necessary scientific evidence relating to, *inter alia*, genotoxic effects of the hormone, to serve as a basis for its ban.[91]

41. The experts disagree with the EC's statement that JECFA's decision to set an ADI for estradiol 17β was affected by its conclusion in its 52nd Report that estradiol 17β has "genotoxic potential". The EC alleges that this finding was critical to JECFA's proposing an ADI for

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[87] *See* Panel's Questions to the Experts, Question 19.

[88] Dr. Boisseau Responses (Question 19), p. 16.

[89] Dr. Boobis Responses (Question 19), p. 22.

[90] Dr. Cogliano Responses (Question 19), p. 2.

[91] As noted in paragraph 39 above, Dr. Guttenplan's response appears to neither endorse or deny the presence of a threshold. His answer does appear to indicate, however, that it would have been possible for the EC to determine a safe level for estradiol 17β, or to have examined the effects of low doses, rather than simply stopping its evaluation once it concluded estradiol 17β is genotoxic. ("The statement that, 'the fact that doses used in growth promotion are low is not of relevance' is not necessarily true. For any toxin the dose determines the risk." "When exposure is very low risk will be very low." Carcinogenic effects are "unlikely if good veterinary practices are followed.") Dr. Guttenplan Responses (Questions 15 and 19), pp. 4-5.

estradiol 17β for the first time in 1999 at its 52nd Meeting.[92] Dr. Boisseau notes, "JECFA's conclusions that oestradiol-17β 'has genotoxic potential' did not affect its recommendation on this hormone."[93] Dr. Boobis agrees, highlighting the rationale behind JECFA's conclusion:

> I do not believe that JECFA's conclusion that oestradiol has "genotoxic potential" affected its recommendations on this hormone, which were based on the conclusion that there was a threshold for its carcinogenic effects. JECFA's conclusion regarding genotoxicity was based on positive results in certain in vitro tests, but the evidence was against a mutagenic response in vivo.[94]

JECFA, in its responses, makes no mention of the finding that estradiol 17β has "genotoxic potential" in its discussion of how its conclusions in 1999 (52nd Meeting) differed from those in 1987 (32nd Meeting).[95] Instead, it notes that its decision to set an ADI for estradiol 17β at its 52nd Meeting was based on consideration of:

> published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of exogenous estrogens. Numerous reports on studies of the use of exogenous estrogens in women were considered, as were studies in experimental animals on the mechanism of action of estradiol-17β. The extensive database derived from the results of epidemiological studies in women taking oral contraceptive preparations containing estrogens or postmenopausal estrogen replacement therapy was also used to evaluate the safety of estradiol-17β.[96]

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[92] The EC avers that JECFA's finding that estradiol 17β "has genotoxic potential" was essential "compared to its previous 1988 evaluation - . . . to [JECFA] propos[ing] the definition of an Acceptable Daily Intake (ADI) for oestradiol 17β, which was not the situation before." EC Answers to Panel Questions, para. 97.

[93] Dr. Boisseau Responses (Question 20), p. 16.

[94] Dr. Boobis Responses (Question 20), p. 23.

[95] JECFA Responses (Question 20), p. 16. JECFA notes that its establishment of an ADI for estradiol 17β (as well as the other two naturally-occurring hormones) was based on "[s]ufficient new data from observations in humans . . . which were suitable to derive ADIs." Rather than the basing its decision to establish an ADI on the finding of the genotoxic potential of estradiol, as argued by the EC, JECFA notes that "the establishment of an ADI implies that there is a threshold of effect for [ ] a compound, below which no[ ] toxicological effects occur." JECFA Responses (Question 20), p. 18.

[96] JECFA Responses (Question 20), p. 16. *See* Dr. Boisseau Responses (Questions 33 and 34), p. 19; Dr. Boobis Responses (Question 33), p. 34; *see also* U.S. First Written Submission, para. 56.

Drs. Cogliano and Guttenplan offer comments on this issue, but neither appears to have addressed the issue (and Panel's question) of whether JECFA's conclusion regarding genotoxic potential affected JECFA's conclusion to set an ADI, as alleged by the EC.[97]

(c) *The scientific evidence does not demonstrate that estradiol 17β will have carcinogenic or tumorigenic effects at concentrations found in meat from cattle treated with hormones for growth promotion purposes*

42. The experts' responses confirm that the scientific evidence cited by the EC in its Opinions does not support the conclusion that estradiol 17β is carcinogenic or tumorigenic at concentrations found in meat from cattle treated with hormones for growth promotion purposes. As noted by Dr. Boisseau, "it is legitimate to conclude that (1) the carcinogenic potential of oestradiol-17β results from its hormonal activity, [and] (2) . . . derive . . . an ADI which represents the highest quantity of oestradiol-17β causing in humans no hormonal effect and therefore no carcinogenic effect."[98] Therefore, Dr. Boisseau concludes that "oestradiol-17β, even [though] it has been recognized as being able to generate tumours, is not likely to produce adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes."[99] Dr. Boobis comments that "an additional factor in the risk assessment of this compound is whether the levels from consumption of meat from treated animals impacts on the circulating levels of the hormone. If not, then there should be no change in risk,"[100] and even "occasional exposure above the ADI, such as might occur if GVP is not followed, would not be associated with any increase in risk of cancer."[101] Dr. Guttenplan appears to agree, noting that while "an adverse effect cannot be ruled out, [ ] it is unlikely if good veterinary practices are followed."[102]

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[97] Dr. Cogliano notes that "the EC's conclusions seem to reflect a concern that endogenous hormone levels are variable," yet also concludes that "the variability of endogenously produced hormone levels is recognized by Codex." Dr. Cogliano Responses (Question 20), p. 2. It is unclear how this statement relates to JECFA's decision making at its 52nd Meeting, and whether or not a finding that estradiol 17β has "genotoxic potential" affected JECFA's ultimate conclusion to set an ADI for the hormone. Dr. Guttenplan appears to have misconstrued the Panel's question, opining that JECFA's conclusion "had some effect on the European Communities' conclusions." Dr. Guttenplan Responses (Question 20), p. 5. This statement is unexceptional, as the EC has consistently argued and attempted to demonstrate that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones. Indeed, it has raised this limited JECFA finding several times in an attempt to support its own decision making. *See*, *e.g.*, EC Answers to Panel Questions, para. 97.

[98] Dr. Boisseau Responses (Question 15), p. 12.

[99] Dr. Boisseau Responses (Question 15), p. 12.

[100] The EC has presented no evidence, for any sector of the human population, that consumption of beef affects circulating (blood) levels of estradiol 17β.

[101] Dr. Boobis Responses (Question 15), p. 18.

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

43. Dr. Cogliano, while noting that the identification of estradiol 17β as a human carcinogen "indicates that there are potential adverse effects on human health"[103] 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,"[104] 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.

44. Lastly, since the metabolism of estradiol 17β to catechol estrogens is a central element of the EC's claim that estradiol 17β is carcinogenic via a genotoxic mechanism, the Panel asked the experts to comment on materials presented by the EC in support of its theory. Although the experts agree that the presence of these metabolites would be important to consider in assessing the genotoxic potential of estradiol 17β, they agree that the materials relied on by the EC failed to detect catechol residues in meat. Dr. Boobis concludes, "[t]he analytical data certainly show that levels of catechol metabolites in meat from treated animals were below the limits of detection of the method."[105] Dr. Boisseau states, "it can be said that this study could not find evidence of metabolites coming from the catechol oestrogen biosynthesis."[106] Finally, Dr. Cogliano concludes "that detectable levels of catechol metabolites were not formed from the parent compound."[107] 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.

(d) *Conclusion*

45. The experts' responses confirm that the scientific evidence cited by the EC in its Opinions does not support the conclusions on estradiol 17β reached by the EC in those Opinions. Therefore, the EC has not based its permanent ban on meat and meat products from cattle treated with estradiol 17β for growth promotion purposes on a risk assessment, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement.[108] Further, the experts' responses confirm that the EC's Opinions have failed to take into account available scientific evidence, as required by Article 5.2 of the SPS Agreement.

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[103] Dr. Cogliano Responses (Question 15), p. 1.

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

[105] Dr. Boobis Responses (Question 17), p. 21.

[106] Dr. Boisseau Responses (Question 17), p. 14.

[107] Dr. Cogliano Responses (Question 17), p. 1.

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

(3) Scientific evidence relating to the five provisionally banned hormones

46. The question of sufficiency of the scientific evidence relating to the five provisionally banned hormones, and the question of what scientific conclusions may be drawn from that evidence are essential to determinations of whether the scientific evidence relating to the hormones was indeed insufficient for the EC to conduct a risk assessment, and whether the EC's provisional bans have been adopted on the basis of available pertinent information within the meaning of Article 5.7 of the SPS Agreement.

47. The experts' responses confirm the following points regarding the scientific evidence relating to the five provisionally banned hormones (progesterone; testosterone; trenbolone acetate; zeranol; and melengestrol acetate): (1) the scientific evidence and information relating to the five hormones is sufficient to conduct an assessment of the risks to human health from consumption of meat from cattle treated with the five hormones for growth promotion purposes; (2) the scientific evidence cited by the EC in its Opinions does not demonstrate that any of the five hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity; and (3) scientific materials produced and cited by the EC (including the "17 Studies") have not identified any gaps or insufficiencies in the scientific evidence such that more study is necessary before the risk from consumption of meat from cattle treated with the five hormones for growth promotion purposes can be assessed.

(a) *The scientific evidence and information relating to the five hormones is sufficient to conduct an assessment of the risks to human health from consumption of meat from cattle treated with the five hormones for growth promotion purposes*

48. The experts' responses confirm that the scientific evidence and information relating to the five hormones is sufficient to conduct an assessment of the risks to human health from consumption of meat from cattle treated with the five hormones for growth promotion purposes. Dr. Boobis states, "[i]n my view there was sufficient information available to the EC to have enabled it to have conducted an assessment of the risks to human health arising from consumption of meat from cattle treated with any of the six hormones at issue."[109] Dr. Guttenplan affirms that JECFA was able to conduct risk assessments for the five hormones, noting that there has been substantial analysis of progesterone, testosterone and MGA. He does note that "[t]here is more limited evidence available" for trenbolone and zeranol,[110] but does not indicate whether this fact would prevent the EC from completing a risk assessment for these hormones. In addition, as one of his reasons for opining that there is more limited evidence available for trenbolone, he notes that it "appears to be significantly estrogenic." The United

[109] Dr. Boobis Responses (Question 61), p. 49.

[110] Dr. Guttenplan Responses (Question 61), p. 13.

States has not been able to locate any evidence supporting this conclusion, as trenbolone is an androgen (mimicking testosterone) and not an estrogen.[111]

49. In relation to the sufficiency of the scientific evidence relating to MGA, the Panel inquired as to whether "nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s," and whether subsequent JECFA reports relied on these same studies. The experts' responses indicate that this is indeed the case,[112] however, as noted by Dr. Boisseau, it is essential to take into account the fact that the dates of studies utilized in an assessment is not as critical a factor as indicated by the EC: "the quality and the number of the available data are more important than the dates at which these data have been produced."[113] As is apparent from Dr. Guttenplan's evaluation of JECFA's assessment of MGA, the quality and quantity of evidence was more than adequate: "[t]he assessment for melengestrol acetate seems sound. Thorough metabolic and estrogenic studies have been carried out."[114] In addition, no new or intervening scientific evidence or studies have cast doubt on the earlier studies relied on by JECFA, further reaffirming that the dates of those studies and data are irrelevant to an evaluation of the safety of the hormone.[115]

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[111] Dr. Guttenplan Responses (Question 61), p. 13. Dr. Guttenplan has failed to cite to any evidence supporting his conclusion on the availability of evidence for trenbolone and zeranol. For example, it may be useful to know what evidence Dr. Guttenplan relies on in concluding that trenbolone is "potentially significantly estrogenic." Dr. Boisseau notes that he does not have the necessary data to answer the question of sufficiency of evidence, but comments that the continual request for more and more data must stop at some point lest the assessment process become "endless." Dr. Boisseau Responses, p. 61.

[112] *See*, *e.g.*, Responses to Questions from the Panel of Dr. Hubert De Brabander ("Dr. De Brabander Responses") (Question 35), p. 10; Dr. Boisseau Responses (Question 35), p. 20.

[113] Dr. Boisseau Responses (Question 34), p. 19.

[114] Dr. Guttenplan Responses (Question 61), p. 13. As a point of clarification on MGA, Dr. Guttenplan indicates in his answer to Question 60 that MGA may be administered as either a feed additive or an implant ("MGA is the only hormone which might be administered by both methods.") This is incorrect – MGA is only administered as a feed additive.

[115] *See* Dr. Boobis Responses (Question 62), pp. 49-58 ("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.")

(b) *Scientific materials cited by the EC in its Opinions do not demonstrate that any of the five hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity*

50. The experts' responses confirm that the scientific materials cited by the EC in its Opinions do not demonstrate or support the conclusion that any of the five hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity. Dr. Boisseau notes for each of the five hormones that, "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of [any of the hormones] are related to a mechanism other than hormonal activity."[116] Dr. Boobis agrees, commenting, "[t]here is no evidence that the hormones testosterone or progesterone have genotoxic potential [and] [t]here is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic. They were negative in a range of tests for genotoxicity."[117] Therefore, "there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals."[118] Dr. Guttenplan's response confirms this conclusion: "[t]here is no conclusive evidence presented by the EC that the five hormones . . . when consumed as residues in meat have genotoxic potential."[119]

(c) *Scientific materials produced and cited by the EC (including the "17 Studies") have not identified any gaps or insufficiencies in the scientific evidence such that more study is necessary before the risk from consumption of meat from cattle treated with the five hormones for growth promotion purposes can be assessed*

51. The experts' responses confirm that the scientific materials produced and cited by the EC (including the "17 Studies") have not identified any substantial gaps or insufficiencies such that more study is necessary before the risk from consumption of meat from cattle treated with the five hormones for growth promotion purposes can be assessed. Dr. Boisseau notes, "[t]hese new [EC] data do not demonstrate any important gaps, insufficiencies and contradictions in the scientific information."[120] Dr. Boobis agrees: "[t]here is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health

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

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

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

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

[120] Dr. Boisseau Responses (Question 62), p. 28.

of consumption of meat . . . can be assessed."[121] Further, "[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."[122]

52. Dr. Guttenplan is the lone expert to identify purported "gaps" in the scientific evidence or data. However, the majority of these alleged gaps in the data appear to relate to estradiol 17β, the hormone for which the EC claims to have completed a risk assessment within the meaning of Article 5.1 of the SPS Agreement as a basis for its permanent ban on meat from cattle treated with estradiol 17β for growth promotion purposes.[123] Dr. Guttenplan's comments do not appear to specifically contemplate the hormones for which one would expect such alleged gaps to exist, *i.e.*, the provisionally banned hormones for which the EC claims insufficient scientific information to complete a risk assessment.[124]

53. The EC has not alleged gaps in the information it has put forward in support of its permanent ban on meat and meat products from cattle treated with estradiol 17β. If a lack of evidence were its reason for banning imports of estradiol-treated meat, due to gaps or insufficiencies, the EC would presumably have included estradiol 17β with the other provisionally-banned hormones. Instead, the EC contends that the evidence and data are clear enough and sufficient to conclude that residues in meat from cattle treated with estradiol 17β for growth promotion purposes pose a health risk to consumers.[125] Regardless, purported data gaps in evidence relating to estradiol 17β have no relevance to the sufficiency of evidence for the five other hormones. Further study can always be done with respect to any scientific issue, and Dr. Guttenplan's response reflects the desire of responsible scientists to have as much information as possible. At the same time, however, Dr. Guttenplan does not say that any of these alleged gaps prevented conducting a risk assessment for any of the hormones.

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[121] Dr. Boobis Responses (Question 62), p. 58.

[122] Dr. Boobis Responses (Question 62), p. 58.

[123] *See* Dr. Guttenplan Responses (Question 62), p. 14. (Dr. Guttenplan identifies "gaps" in the following areas: estrogen levels in children; identification and quantification of lipoidal esters; and matched population studies comparing various populations of children).

[124] Further clarification would be necessary to determine whether Dr. Guttenplan was of the opinion that data "gaps" existed for any of the five provisionally-banned hormones.

[125] *See*, *e.g.*, EC First Written Submission, para. 17 ("[The EC's ban] is based on a comprehensive risk assessment and, thus, is fully compliant with the DSB recommendations and rulings. In particular, as stipulated by the Appellate Body, the results of the risk assessment 'sufficiently warrant' the definite import prohibition regarding one of the hormones (Article 5.1 of the SPS Agreement).")

(d) *Conclusion*

54. The experts' responses confirm that the scientific evidence or information relating to the five provisionally banned hormones is indeed sufficient (or rather, not insufficient) for the EC to have completed a risk assessment for each of the hormones. Further, the experts' responses confirm that the EC's provisional bans have not been adopted on the basis of available pertinent information within the meaning of Article 5.7 of the SPS Agreement because the available pertinent information indicates that consumption of residues of the hormones in meat from cattle treated for growth promotion purposes is safe for consumers. In short, the EC has not implemented provisional bans for any of the five hormones that satisfy the cumulative conditions of Article 5.7 of the SPS Agreement.

(4) Scientific evidence relating to the hormones generally

55. An evaluation of the scientific evidence relating to the six hormones generally is essential to a determination of whether, on the one hand, the EC has completed a risk assessment for estradiol 17β within the meaning of Article 5.1 and whether that assessment takes into account available scientific evidence within the meaning of Article 5.2 of the SPS Agreement, and on the other hand whether the EC has implemented a provisional ban for the other five hormones within the meaning of Article 5.7 of the SPS Agreement.[126] Several of the Panel's questions ask the experts to opine on the state of the scientific evidence relating to the six hormones generally.

56. The experts' responses confirm the following points regarding the scientific evidence relating to the hormones generally: (1) each of the hormones has been used for growth promotion purposes in cattle and evaluated for a sufficient period of time with no evidence of adverse effects to adequately address any concern regarding long latency periods of cancer; (2) epidemiological studies cited by the EC do not identify a link between cancer and residues of the hormones in meat; (3) the EC has failed to demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations; and (4) the EC has failed to demonstrate "other risks" to human health from consumption of residues of the hormones in meat from cattle treated for growth promotion purposes, such as effects on the immune system.

[126] Note that the majority of the essential questions regarding the state of the scientific evidence relating to the six hormones has already been addressed above in the discussions of estradiol 17β and the five provisionally banned hormones.

(a) *Each of the hormones has been used for growth promotion purposes in cattle and evaluated for a sufficient period of time with no evidence of adverse effects to adequately address any concern regarding long latency periods of cancer*

57. The experts' answers confirm that, while it is necessary to take into account the long latency period of cancer in evaluating the safety of the six hormones, each of the hormones has been used for growth promotion purposes in cattle and evaluated for a sufficient period with no evidence of adverse effects to consumers to adequately address this concern.[127] Dr. Boobis notes, "the latency period is an important consideration," but confirms that studies of animals and humans "cover[ ] a sufficiently long period to encompass the latency period for any carcinogenic effects of the hormones."[128] Further, "[t]he long term studies of the hormones undertaken in experimental animals and in humans, involved much higher doses than would be encountered on consumption of meat from animals treated with growth promoting hormones."[129]

58. Dr. Boobis notes the difficulty in distinguishing results among effects from hormone residues in food, naturally-occurring hormones and other factors, but agrees that "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."[130] Dr. Guttenplan concurs that hormones have been consumed in meat for a "sufficient number of years to observe strong or moderate increases in risk."[131] Yet, as described in detail in the discussion of epidemiological studies and recent materials cited by the EC below, there is no evidence of such increases.

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[127] Dr. Cogliano notes the importance of considering latency periods, and cites IARC materials indicating that a period of at least twenty years should be taken into account. Dr. Cogliano Responses (Question 23), p. 2. The three naturally-occurring hormones at issue in this dispute have been consumed as residues in meat for millenia without evidence of adverse effects on human health. All of the hormones have been consumed as residues in meat from cattle treated for growth promotion purposes for longer than twenty years.

[128] Dr. Boobis Responses (Question 23), p. 26.

[129] Dr. Boobis Responses (Question 23), p. 26.

[130] Dr. Boisseau Responses (Question 23), p. 17.

[131] Dr. Guttenplan Responses (Question 23), p. 7.

(b) *Epidemiological studies cited by the EC do not identify a link between hormone residues in meat and cancer*

59. The experts' responses confirm that the epidemiological studies cited by the EC in its Opinions fail to identify a link between hormone residues in meat and cancer.[132] Dr. Guttenplan concludes, "[t]he epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters."[133] As noted by Dr. 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."[134] Indeed, the correlation lies not between hormone residues and cancer, but instead the association with cancer "is strongest with meat consumption and show[s] little relationship with whether the meat is from animals treated with growth promoting hormones or not."[135]

60. Dr. Boisseau cites back to an earlier response in which he comments, "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 from the treatment of cattle with growth promoters."[136] Dr. Cogliano agrees, stating that "[t]he difference between the U.S. and the EC in rates of breast cancer and prostate cancer almost certainly has multiple causes," and that while it is "possible that differences in exposure to exogenous hormones can be one cause, [ ] the data are not sufficiently specific to establish a link between these observations."[137]

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[132] Confounding factors play a role in the evaluation of epidemiological data. The experts are split as to whether these factors can be identified and their effects attributed to a particular source. *See* Dr. Boisseau Responses (Question 24), p. 17. However, there is agreement that such factors exist, and that they should be taken into account in the interpretation of data used in a risk assessment. *See* Dr. Boobis Responses (Question 24), p. 27; Dr. Cogliano Responses (Question 24), p. 2; Dr. Guttenplan Responses (Question 24), p. 9 ("These are important considerations for risk assessment of adverse affects caused by residues of growth promoting hormones in meat, as the effects of the hormones (if any) are likely to be small and might be obscured by confounders.") None of the experts express the opinion that the EC's Opinions took confounding factors into account in the assessment of the safety of the hormones.

[133] Dr. Guttenplan Responses (Question 26), p. 9. Dr. Guttenplan also notes that "[t]he references to the higher rates of breast cancer and prostate cancer observed in the United States as compared to the [EC] are not very convincing," and that "the differences in rates of breast cancer and prostate cancer . . . are relatively small." Dr. Guttenplan Responses (Question 24), p. 9.

[134] Dr. Boobis Responses (Question 26), p. 32.

[135] Dr. Boobis Responses (Question 26), p. 32.

[136] Dr. Boisseau Responses (Question 26), p. 17, *citing* earlier responses on pp. 16-17.

[137] Dr. Cogliano Responses (Question 26), p. 2.

61. The experts' comments on epidemiological studies are linked to another of the Panel's questions, namely whether three studies recently cited by the EC demonstrate a risk to human health from the consumption of meat from cattle treated with hormones for growth promotion purposes. The experts agree that the three studies demonstrate no such risk. Dr. Boobis concludes that none of the studies confirm a risk to human health from the consumption of meat from cattle treated with hormones for growth promotion purposes.[138] Dr. Guttenplan agrees, noting that in the first study "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."[139] Regarding the second and third studies, Dr. Guttenplan simply comments that "the other two studies do not confirm a risk from hormone-treated meat."[140] He also notes that, "[t]he [EC] statement that one of the studies was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, negates any relevance to the possible connection of hormone-treated meat consumption and cancer."[141]

62. Dr. Boisseau cites back to earlier responses, restating his conclusion that "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,"[142] as evidence of his opinion that the first EC study provided no such evidence. Regarding the second study, Dr. Boisseau restates his conclusion that epidemiological studies in humans have failed to identify a relationship between tumors and the consumption of meat from treated cattle, thereby indicating his opinion that this new study demonstrates no such link.[143] Finally, Dr. Boisseau notes that despite the EC's concern regarding the alleged risk of cancer from meat from cattle treated with hormones for growth promotion purposes, the EC has not "provide[d] any scientific evidence supporting this concern."[144]

63. The final expert, Dr. Cogliano, appears to support the conclusions of the other experts, noting that "[t]he study by Norat et al (2005) indicates a risk to human health from the consumption of meat."[145] As noted above, this conclusion is unexceptional, as it is not evidence

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[138] *See* Dr. Boobis Responses (Question 25), pp. 29-31.

[139] Dr. Guttenplan Responses (Question 25), p. 9.

[140] Dr. Guttenplan Responses (Question 25), p. 9.

[141] Dr. Guttenplan Responses (Question 25), p. 9.

[142] Dr. Boisseau Responses (Question 25), p. 17.

[143] *See* Dr. Boisseau Responses (Question 25), p. 17. Dr. Boisseau notes that the third study is out of his scope of expertise.

[144] Dr. Boisseau Responses (Question 25), p. 17.

[145] Dr. Cogliano Responses (Question 25), p. 2.

of a risk from residues in meat from cattle treated with any of the six hormones for growth promotion purposes, but rather relates to meat consumption generally.[146] For example, as described in paragraph 59 above, Dr. Boobis agrees that the correlation between consumption of meat and any cancer risk lies not between hormone residues and cancer, but instead "is strongest with meat consumption and show little relationship with whether the meat is from animals treated with growth promoting hormones or not."[147] As for the remaining two studies, Dr. Cogliano concludes that the studies merely "suggest a risk to human health," and clarifies his response by noting that the word "suggest" is used instead of "indicates" because "the exposure levels in these studies are higher than those found in meat residues."[148]

(c) *The EC has failed to demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations*

64. The experts' responses indicate that the EC has failed to demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations because: (1) the assay relied upon by the EC to demonstrate lower circulating estradiol 17β levels in children has not been validated; (2) the EC has not demonstrated that exposure to estradiol 17β residues in meat from cattle treated with hormones for growth promotion purposes presents a potential risk to prepubertal children or other sensitive populations; and (3) the materials cited by the EC do not place into doubt Codex conclusions on the safety of the hormones.

1. <u>The assay relied upon by the EC to demonstrate lower circulating estradiol 17β levels in children has not been validated</u>

65. The experts' responses confirm that it is critical that assays be validated before they are used as the basis for conclusions in a risk assessment.[149] Yet, no evidence has been presented demonstrating that the assay for estradiol 17β relied on by the EC, the Klein assay,[150] has been

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[146] *See* Dr. Boobis Responses (Question 26), p. 32.

[147] Dr. Boobis Responses (Question 26), p. 32.

[148] Dr. Cogliano Responses (Question 25), p. 2.

[149] *See* Dr. Boisseau Responses (Question 38), p. 21 ("It would be important to know wether these new bioassays have been properly validated as this SCVPH Opinion says nothing about that and whether the data obtained with these methods for both men and women are also totally different from those obtained with the RIA methods.")

[150] The EC's own CVMP concludes the following regarding the Klein assay: "It was noted that the report by Klein et al. (1994) indicated much lower plasma levels of oestradiol when measured with a new method, based on -galactosidase gene expression in genetically modified yeast, compared to the classical RIA requirements (Klein et al., 1994). However, (i) the measure was made only in plasma and needs to be carried out in other tissue(s) to enable

properly validated since it was first used in 1994. As noted by Dr. Boobis, the original Klein assay (1994) "reported very low levels of oestradiol in male children . . ., but in a later study (Klein et al, 1998), the same group reported mean levels somewhat higher, at 0.27 pg/ml. The reliability of the Klein et al assay has yet to be determined."[151] Dr. Boobis comments, "[t]he assay is particularly sensitive to oestradiol, but there is no obvious explanation for this, as it relies on the affinity for the oestrogen receptor."[152] When compared to other results from yeast-based assays, it is clear that "results with the yeast reporter assay are not consistent, and use of such data in risk assessment requires that the assay be adequately validated."[153]

66. An important step in assay validation is confirmation of the results reported by the original author(s) by scientists in another, independent laboratory. Dr. Sippell notes that the "validity of the [Klein assay] has now been confirmed by another [assay] of E2 [estradiol 17β] which was developed by Charles Sultan's group at the University of Montpellier, France (Paris et al 2002). Unfortunately, the complexity of the [assay] so far prevents its wider use for routine measurements in small serum samples from infants and prepubertal children."[154] However, the Klein assay and Paris assay cited by Dr. Sippell differ in significant ways, and it cannot be stated that the latter independently confirms the results of, or validates the former. For example, the two assays employ different media – the Klein assay utilizes yeast cells and the Paris assay mammalian cells (a human cancer cell line (HeLa cells)). In addition, the Paris assay reflects circulating levels of estradiol 17β at least an order of magnitude greater than those identified in the 1994 Klein assay.[155] In order to conclude that the work of Paris validated the assay relied on by the EC in its Opinions, there would have to be congruity in the results of the assays. Therefore, the EC has based conclusions in its Opinions on hormone levels in sensitive populations on an assay that has not been properly validated.

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to comparison between the intake of residual oestradiol and the endogenous levels, [and] (ii) the methodology needs validation and is not (yet) generally accepted." CVMP (1999), *Report of the CVMP on the Safety Evaluation of Steroidal Sex Hormones in particular for 17β-Oestradiol, Progesterone, Altrenogest, Flugestone acetate and Norgestomet in the Light of New Data/Information made available by the European Commission* (EMEA/CVMP/885/99) ("1999 CVMP Report"). (Exhibit US-5). *See* 1999 EC Opinion, § 2.2.2.1 ("Physiological levels of steroids in serum during childhood and puberty"), p. 11; Table 1, p. 28. (Exhibit US-4).

[151] Dr. Boobis Responses (Question 40), p. 37.

[152] Dr. Boobis Responses (Question 40), p. 37.

[153] Dr. Boobis Responses (Question 40), p. 37.

[154] Responses of Dr. Wolfgang Sippell ("Sippell Responses") (Question 40), p. 2.

[155] *See* Dr. Boobis Responses (Question 40), p. 39.

2. The experts' responses confirm that the EC has failed to demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations

67. The experts' responses do not support the conclusion that exposure to estradiol 17β residues in meat from cattle treated with hormones for growth promotion purposes presents a risk to prepubertal children or sensitive populations. Indeed, one of the experts notes that the EC has failed to assess this risk entirely.[156] Another notes that the materials put forward by the EC require no changes in the JECFA and Codex standards relating to the growth promoting hormones.[157] One of the experts, Dr. Sippell, disagrees; however, in so doing, Dr. Sippell's responses propose several conclusions regarding sensitive populations that are both unresponsive to the Panel's questions and unsupported by the scientific material cited in his answers. Relying on the (unvalidated) Klein assay,[158] Dr. Sippell's responses postulate that circulating levels of estradiol 17β in children are "100 times lower" than previously thought, and that the "resulting potential E2 [estradiol 17β] exposure risk from consumption of meat and meat products has greatly increased by a factor of at least 160 times."[159] Dr. Sippell draws the following additional conclusions regarding sensitive populations:

> [i]t has been shown in numerous scientific publications in vitro, in vivo and in the human that infants and prepubertal children are highly sensitive to increased E2-levels, resulting in premature breast development (Schmidt et al 2002), growth acceleration (Lampit et al 2002), earlier sexual maturation in girls, in particular in the USA (Sun et al 2002, Wu et al, 2002) and less in Europe (Muinck-Keizer & Mul 2001), and the well known significantly higher incidence of precocious puberty in girls than in boys (Teilmann et al 2005). Accidental exposure of prepubertal boys to estrogen has resulted in gynecomastia and advanced bone maturation.[160]

The materials cited by Dr. Sippell do not appear to be responsive to the Panel's question, which sought comment on the EC statement that "any excess exposure" to estradiol 17β resulting from the consumption of meat presents a potential risk to public health in particular sensitive populations such as prepubertal children. None of the citations made by Dr. Sippell address this specific question, nor do the studies cited by Dr. Sippell present any evidence that the low levels of estradiol 17β residues in beef (from either treated or untreated cattle) would be sufficient to

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[156] *See* Dr. Boisseau Responses (Question 39), pp. 21-22.

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

[158] *See* Dr. Boobis Responses (Question 40), p. 37 ("use of such data in risk assessment requires that the assay be adequately validated.")

[159] Dr. Sippell Responses (Question 39), p. 1.

[160] Dr. Sippell Responses (Question 39), p. 1.

affect the health or development of prepubertal children. Further, Dr. Sippell's responses appear to propose a different result than his own research, in which he has concluded "[a]lthough there is concern that oestrogen consumption through food might have adverse effects on pubertal development and human health, there are no published data to support the notion that an increased overall exposure to environmental oestrogens has led to an increased incidence in precocious puberty or to an earlier start of pubertal development."[161]

68. The Schmidt study cited by Dr. Sippell as evidence of premature breast development concludes that the stimulation of the mammary gland by estradiol 17β in infancy may represent a window that is of biological significance for breast development in adulthood. However, the Schmidt study is not relevant to the analysis at hand nor germane to the Panel's question, as the authors characterize their findings as physiologic, *i.e.*, normal. The study does not describe any pathologic findings (as implied by Dr. Sippell's use of the phrase "premature breast development") and it was simply not designed to examine the relationship between breast tissue in infants and dietary estradiol 17β (*i.e.*, the form of estrogen of relevance to the consumption of meat).

69. Dr. Sippell also cites a study by Lampit *et al*. to support his theory that estradiol 17β residues in meat from cattle treated for growth promotion purposes will cause "growth acceleration". The Lampit study examined girls with central precocious puberty, and demonstrated that a "mini-dose" of estradiol 17β maintained normal pubertal growth in the girls. However, the results of the study cannot be extrapolated to the conclusion that estradiol 17β residues in meat will cause growth acceleration in sensitive populations. For instance, any results obtained in patients with endocrine disorders such as central precocious puberty must be extrapolated with great caution because the function of their reproductive axis is fundamentally different from normal children, and it is possible that their sensitivity to estradiol 17β is altered compared to normal children. More importantly, the Lampit study fails to quantify the amount of estradiol 17β (either endogenous or exogenous) that would be required to accelerate growth in normal children and similarly fails to demonstrate a risk of accelerated growth due to dietary consumption of estradiol 17β.

70. The Sun paper involved a large-scale study of sexual development in white, black and Mexican-American children in the United States. The study, which presents national reference data, concluded that non-hispanic black girls and boys had earlier ages for sexual maturity compared to the other two groups. The paper is limited to statistics on children in the United States and makes no effort to compare these data to those for European children. It is therefore unclear how Dr. Sippell reaches his conclusion that this phenomenon occurs "in particular in the USA and less in Europe."[162] In any event, the study does not examine or measure estradiol 17β

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[161] Partsch and Sippell, *Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens*. Hum Reprod Update 2001; 7: 292-302. (Emphasis added).

[162] Dr. Sippell Responses (Question 39), p. 1.

at all, and therefore cannot be used as evidence in support of Dr. Sippell's conclusion that exposure to estradiol 17β results in "earlier sexual maturation in girls, in particular in the USA."[163] The Wu paper uses the same data set as the Sun paper, concluding that black and Mexican-American girls reach puberty at younger ages than white girls. As is the case with the Sun paper, Wu simply does not support the conclusions extrapolated from it by Dr. Sippell. Further, there is absolutely no evidence in either the Sun paper or the Wu paper to suggest that the observed differences in age of puberty may be attributable to the presence of estradiol 17β residues in meat.

71. The de Muinck Keizer-Schrama and Mul review article (2001) concludes that the age of puberty in Europe decreased over the last century, but that in recent decades this decrease has slowed. No scientific evidence is provided to definitively identify the basis for these changes, but the authors cite socioeconomic conditions and better health care and prevention as the "most important factors." Possible dietary influences on age of puberty in Europe, including animal protein, saturated fat, dairy products and phytoestrogens are also discussed. The de Muinck Keizer-Schrama review fails to present any evidence indicating that estradiol 17β residues in meat have had any influence on the age of puberty in either Europe or the United States.

72. The Teilmann article concludes that the prevalence of precocious puberty[164] in Denmark was very low (< 1 in 10,000); that it was higher in girls than in boys; and that the rate was constant between 1993 and 2001. However, the Teilmann study does not provide any evidence supporting Dr. Sippell's conclusion that high sensitivity to increased estradiol 17β levels results in higher incidences of precocious puberty in girls than in boys. The cause of precocious puberty is not only unknown, it was not even examined by the authors of the Teilmann paper.

73. Finally, the Felner and White paper examined three prepubertal boys with gynecomastia, each of whom was exposed to an estrogen cream used by his mother. All three boys had elevated blood levels of estradiol 17β, which returned to normal once their mothers stopped using the cream. The authors concluded: "[i]ndirect exposure to excessive amounts of topical estrogen may cause gynecomastia, rapid changes in growth, and advanced bone age in prepubertal children."[165] It is not possible to extrapolate data involving exposure to "excessive amounts" of estrogen cream to conclusions regarding estradiol 17β residues in meat from cattle treated for growth promotion purposes. Further, exposure to estradiol 17β in the Felner and White paper was transdermal, a method of administration that bypasses the extensive first pass metabolism of estradiol 17β and thus results in much higher levels of exposure than those that

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[163] Dr. Sippell Responses (Question 39), p. 1.

[164] In this study, precocious puberty was defined as onset of puberty before nine years of age in girls and ten years of age in boys.

[165] Felner and White, *Prepubertal gynecomastia: indirect exposure to estrogen cream*. Pediatrics 105 (2000), E55. (Emphasis added).

follow oral administration of estradiol 17β (the applicable route for consumption of estradiol 17β residues in meat).

74. Dr. Sippell also concludes, "[t]here is now increasing epidemiological evidence that exposure to elevated estrogen levels during early life (pre- and postnatally) carries an increased risk of breast cancer in adult life, whereas conditions with low E2 levels, such as preeclampsia seem to have a protective effect."[166] Dr. Sippell cites to eight papers in support of this statement, yet none of the papers appears to demonstrate that the conclusion is correct or responsive to the Panel's question. For instance, four of the papers (Ekbom (1997); Swerdlow (1997); Weiss (1997); and Innes and Byers (1999)) are all human epidemiological studies that purport to document a higher risk of breast cancer in adult twins (who may have been exposed to higher levels of estradiol 17β in utero compared to singletons) and a lower risk of breast cancer in women whose mothers had preeclampsia (which may be associated with lower estradiol 17β levels compared to normal pregnancies). However, the findings of each of these studies are based entirely on correlation/assumption, without any mechanistic evidence. The fifth paper, by Halkavi-Clarke *et al*., is a rat study showing that in utero exposure to tamoxifen[167] increases susceptibility to breast cancer (induced by treatment with the carcinogen DMBA). The results of this study are difficult to interpret, in that tamoxifen has mixed estrogen agonist/antagonist activity; confounded because tamoxifen caused abnormal reproductive development; and not relevant to a discussion of the potential effects of estradiol 17β from the consumption of meat and meat products (and therefore not responsive to the Panel's question).

75. In addition, Dr. Sippell concludes from the remaining three papers that "indirect evidence suggests that male reproductive disorders such as testicular cancer, cryptorchidism, hypospadias and poor sperm quality may also have their origin in hormonal disturbances induced by E2 and/or estrogenic substances during fetal life (Skakkebaek et al 2001) and also during childhood (Higuchi et al 2003, Ramaswamy 2005)."[168] Again, Dr. Sippell's conclusion, premised on "indirect evidence" that "may" demonstrate an effect, is not supported by the cited evidence nor responsive to the Panel's question.

76. For instance, the Skakkebaek paper speculates that "[testicular dysgenesis syndrome] is a result of disruption of embryonal programming and gonadal development during fetal life." However, support for this claim is limited to animal studies involving in utero exposure to synthetic compounds such as DES and ethinyl estradiol, but not estradiol 17β or any of the other hormones used for growth promotion purposes in cattle.[169] There is ample evidence in animal

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[166] Dr. Sippell Responses (Question 39), pp. 1-2.

[167] Tamoxifen is a drug which has been used in humans to treat breast cancer.

[168] Dr. Sippell Responses (Question 39), p. 2.

[169] The fact that synthetic estrogens were used in these studies is an important distinction because the bioavailability of these estrogens is much higher than the bioavailability of estradiol 17β.

studies that, at levels of exposure greater than the levels found in meat residues from treated cattle, in utero exposure to estrogen can affect the development of the male fetus. However, it must be emphasized that this is only the case when exposure levels are orders of magnitude greater than those relevant to an analysis of residues in meat from cattle treated with hormones for growth promotion purposes.[170] Further, evidence for latent or delayed effects on adult reproductive function caused by exposure to hormones is limited at best and confounded by numerous other factors. Dr. Sippell appears to acknowledge this by noting that the evidence is (at best) "indirect."

77. The Higuchi paper reports that the reproductive function of adult male rabbits was impaired following in utero exposure to dibutyl phtalate (DBP), a plasticizer and well known reproductive toxicant. The authors assume that these effects were due to a direct toxic effect on the testis, not the alteration of the endocrine milieu as suggested by Dr. Sippell's response. Moreover, and perhaps of greater significance to the analysis at hand, the study focuses on the effects of a compound (DBP) unrelated to the hormones at issue (such as estradiol 17β or zeranol). DBP's estrogenic potency appears to be very low relative to estradiol 17β,[171] and it has been shown to have anti-androgenic effects which may be more adverse than its estrogenicity.[172] Therefore, it seems highly likely that the mechanism of toxicity of DBP does not involve "hormonal disturbances", contrary to the conclusion reached by Dr. Sippell.

78. The final paper by Ramaswamy has very limited applicability to possible risks associated with the consumption of residues in meat from cattle treated with hormones for growth promotion purposes, and therefore limited applicability to the Panel's question. The Ramaswamy study involved subcutaneous administration of estradiol 17β (not oral as is the case with consumed residues, thereby bypassing extensive first pass metabolism in the intestine and liver); doses of estradiol 17β that were much higher than those that could be derived from consumption of beef; and ~40-fold elevations in blood estradiol 17β that were sustained for 5-20 weeks, a situation that is not comparable to the intermittent, low-level exposure to estradiol 17β which might occur due to consumption of meat.

79. Finally, in response to the Panel's inquiry of how risks for individuals arising from "hormones naturally present in meat differ from risks arising from the residues of hormone growth promoters," Dr. Sippell concludes that "[s]ynthetic hormone growth promoters such as

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[170] Here, Dr. Sippell is making an unsubstantiated extrapolation to suggest that adverse effects caused by very high levels of estradiol 17β in animal studies may also occur in humans.

[171] Milligan SR *et al*., *Relative potency of xenobiotic estrogens in an acute in vivo mammalian assay*. Environ Health Perspect 106: 23-26 (1998).

[172] Leffers *et al*., Hum Reproduction (2001); 16: 1037-1045 (one of the "17 Studies"). Also, a yeast-based assay has shown that DBP's estrogenic potency is 1,000,000-fold lower than estradiol 17β, and that there is no estrogenic ability in DBP in an in vivo assay using ovariectomized mice. *See* Ohtani H *et al*., Environmental Health Perspectives (2000); 108; 1189-1193.

Zeranol and its metabolites have been shown to be as potent as E2 and [DES] in increasing the expression of estrogen-related genes in human breast cancer cells (Leffers et al 2001). On the other hand, the synthetic androgen Trenbolone and gestagen Melengestrol bind with high affinity to the human androgen and progesterone receptors, respectively (Bauer et al 2000)."[173] No scientific evidence is cited by Dr. Sippell to support his conclusion that "[e]xposure during pregnancy might result in sever transplacental virilisation of a female fetus."[174] Dr. Sippell's response appears to misconstrue the Panel's question, in that it discusses the hypothetical effects of synthetic hormones rather than discussing the differences in naturally-present hormone levels as compared to residue levels resulting from the use of hormones as growth promoters.

80. Dr. Sippell appears to be of the opinion that the potential risk from synthetic hormones may differ from hormones naturally present in meat because the synthetics are more potent than their natural counterparts. For instance, he cites to a paper by Leffers (one of the EC's "17 Studies") in support of the statement that zeranol, estradiol 17β and DES are equipotent. However, as is the case with most of the in vitro studies cited by the EC, the physiological relevance of the Leffers findings is questionable because: (1) the assay utilized a breast cancer cell line (MCF-7) which may not accurately reflect the sensitivity of normal breast tissue to estrogens (*e.g.*, estrogen receptor populations may differ between MCF-7 and normal breast cells); and (2) there are numerous reports in the literature demonstrating that DES is more potent than estradiol 17β, yet inexplicably, they register as equipotent in the Leffers paper. Furthermore, the Leffers paper simply does not provide evidence pertinent to the question at hand, *i.e.*, whether zeranol residues in beef present a risk to sensitive populations that is different from the risks arising from hormones naturally present in beef.

81. The Bauer study is also one of the "17 Studies" commissioned by the EC. In the Bauer study, the primary metabolite of trenbolone acetate found in bovine muscle (17β-TBOH) bound to the human androgen receptor with high affinity. While this finding raises the specter that residues of trenbolone acetate in meat may be androgenic in humans, Dr. Sippell does not provide any scientific evidence demonstrating that this is the case. On the contrary, the evidence presented thus far indicates that an androgenic effect of such residues is highly unlikely due to their extremely low levels in meat and poor bioavailability. In addition, Bauer *et al*. measured the binding of MGA and MGA metabolites to the bovine progesterone receptor, not the human receptor. Therefore, Dr. Sippell's statement that MGA binds with high affinity to the human progesterone receptor is unsupported by the citation to the Bauer study.

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[173] Dr. Sippell Responses (Question 41), p. 3. In addition, Dr. Sippell notes that "[the increased percentage of estradiol 17β consumed in meat from treated as opposed to untreated cattle], and thus the potential health risk, will be considerably higher if the food intake from pork, poultry, eggs and dairy products derived from E2 -treated farm animals are taken into account." However, estradiol 17β is not used for growth promotion purposes in poultry or pork. *See* Dr. Sippell Responses (Question 41), p. 3.

[174] Dr. Sippell Responses (Question 41), p. 3.

82. In summary, none of the papers cited by Dr. Sippell support the conclusion that exposure to estradiol 17β in meat from cattle treated with hormones for growth promotion purposes presents a potential risk to prepubertal children or sensitive populations. In particular, none of the studies present evidence that the extremely low amounts of estradiol 17β in meat are sufficient to affect the health or development of prepubertal children.

3. The materials cited by the EC do not place into doubt Codex conclusions on the safety of the hormones

83. The experts' responses confirm that the materials cited by the EC do not place into doubt Codex conclusions on the safety of the six hormones. Dr. Boobis opines that, even if circulating estradiol 17β levels in prepubertal children are lower than previously contemplated,[175] the JECFA ADI for estradiol 17β would still "appear to be appropriate for all groups of the population,"[176] including prepubertal children. Dr. Boobis notes that several intervening steps and factors must be considered in an assessment of any risk to this population: "this exposure is via the oral route, and bioavailability by this route is very low (<5%) (Fortherby 1996). In addition, very little of the absorbed hormone will be free, over 95% being bound to plasma proteins such as SHBG. Such binding reduces the biological activity of the hormone (Teeguarden and Barton, 2004)."[177] Therefore, even if an assay indicates that circulating estradiol 17β levels are lower, reliance on this fact alone does not suffice to assess any potential risk.

84. Further, as has been discussed in detail in the experts' responses, JECFA has taken into account additional safety factors in order to adequately compensate for the lower circulating levels of hormones in sensitive populations such as prepubertal children. As noted by Dr. Boobis, JECFA employs a 10-fold safety factor to protect sensitive populations and another 10-fold adjustment for inter-individual variation.[178] In other words, "[i]n keeping with its risk

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[175] The experts appear to agree that results obtained using the estradiol 17β assay reported by Paris *et al.* (2002) are worthy of further consideration. However, this assay also requires further validation. The Paris assay was not used to estimate estradiol 17β levels in the EC's Opinions; rather the EC used data from the unvalidated Klein assay, which estimated estradiol 17β in prepubertal children at levels at least an order of magnitude less than the levels of the Paris assay. *See* 1999 EC Opinion, § 2.2.2.1, p. 11; Table 1, p. 28.

[176] Dr. Boobis Responses (Question 40), p. 39.

[177] Dr. Boobis Responses (Question 40), p. 39.

[178] Dr. Boobis Responses (Question 42), p. 39. Dr. Boisseau confirms that JECFA "has considered appropriate to establish a NOAEL on the basis of the changes in several hormone dependent parameters in post menopausal women and to derive from this NOAEL an ADI using two safety factors of 10, one to account for normal variation among individuals and a second one to protect the sensitive human populations." Dr. Boisseau Responses (Question 13), p. 9. Note that the EC's CVMP, in determining the estradiol 17β is safe for use for zootechnical and therapeutic purposes in cattle "based its risk assessment on the relation between any possible excess of hormones from zootechnically treated animals in the diet and the endogenous daily production of

assessment principles, the ADI established by JECFA would have been designed to protect all segments of the population, including prepubertal children."[179] Therefore the ADI for estradiol 17β has a 100-fold safety factor built in. Dr. Boisseau concurs that JECFA took into account sensitive populations in its risk assessments, and notes, "[f]rom a qualitative point of view, the risks for these individuals arising from residues resulting from the use of hormones as growth promoters in cattle does not differ from the risks arising from the residues of hormones naturally present in meat. The potential problem which may exist is only a quantitative one."[180]

85. According to Dr. Boisseau, this information was not taken into account by the EC in its purported risk assessment. He comments, "[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 by growth promoters, from other food and products of animal origin and from their own production of hormones."[181] Dr. Boobis concludes, "there is no requirement for any revision in the Codex recommendation with respect to oestradiol-17β on the basis of the material referred to by the EC."[182]

(d) *The scientific evidence cited by the EC fails to demonstrate adverse effects on the immune system or "other risks" to human health from the consumption of meat from cattle treated with the growth promoting hormones at issue*

86. The experts' responses confirm that the scientific evidence cited by the EC fails to demonstrate adverse effects on the immune system or "other risks" to human health from the consumption of meat from cattle treated with the growth promoting hormones at issue. Dr. Boobis states, "[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."[183] He notes that "[g]iven the large margin of exposure on anticipated intake from residues in meat from treated animals, no effect on the immune system is anticipated, as immune

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oestradiol in prepubertal boys." 1999 CVMP Report, p. 12. (Exhibit US-5). Dr. Sippell disagrees that JECFA has adequately taken into account sensitive populations, but it is unclear from his response if he is familiar with JECFA's safety factors or whether/why he finds these factors to be inadequate. Dr. Sippell Responses (Question 42), p. 3.

[179] Dr. Boobis Responses (Question 42), p. 39.

[180] Dr. Boisseau Responses (Question 41), p. 22.

[181] Dr. Boisseau Responses (Question 39), pp. 21-22.

[182] Dr. Boobis Responses (Question 42), p. 39.

[183] Dr. Boobis Responses (Question 59), p. 48.

modulation is dependent on dose and there are thresholds for such effects."[184] Dr. Guttenplan notes that, while there is evidence that estrogens generally can be related to certain disorders, "[n]o definitive studies have related intake of meat from hormone-treated animals to the above disorders."[185] Finally, Dr. Boisseau comments that, while the evidence cited by the EC would permit it to identify potential adverse effects (*i.e.*, hazard identification), the EC has performed no assessment of potential effects relating to the consumption of residues in meat from treated cattle, and it is therefore "not possible to conclude that this scientific evidence allows to identify any adverse effects on the immune system associated with the consumption of meat from cattle treated with the growth promoters at issue."[186]

(e) *Conclusion*

87. The experts' responses confirm that the scientific evidence relating to the six hormones generally demonstrates that the hormones have been studied for sufficient time to take into account latency periods for cancer; that epidemiological studies do not demonstrate a link between residues of hormones in meat and cancer; that the EC has failed to demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations; and that the EC has failed to demonstrate "other risks" from consumption of residues of the hormones in meat from cattle treated for growth promotion purposes, such as effects on the immune system. Therefore, the experts' responses demonstrate that the EC has failed to base its permanent ban on meat treated with estradiol 17β on a risk assessment within the meaning of Article 5.1 of the SPS Agreement and that the EC's Opinions have failed to take into account available scientific evidence within the meaning of Article 5.2 of the SPS Agreement. Further, the experts' responses demonstrate that the EC's provisional bans have not been adopted on the basis of available pertinent information within the meaning of Article 5.7 of the SPS Agreement.

(5) Scientific evidence relating to residues

88. The scientific evidence relating to residues in meat from cattle treated with any of the six hormones for growth promotion purposes is relevant to the obligation in Article 5.1 of the SPS Agreement that Members must base their measures on a risk assessment, as appropriate to the circumstances, as well as Article 5.2's requirement that risk assessments take into account available scientific evidence. The scientific evidence relating to hormone residues is also relevant to Article 5.7 of the SPS Agreement and an analysis of whether the EC's provisional ban is based on available pertinent information.

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[184] Dr. Boobis Responses (Question 59), p. 48.

[185] Dr. Guttenplan Responses (Question 59), p. 13.

[186] Dr. Boisseau Responses (Question 59), p. 27.

89. The experts' responses support the following conclusions regarding the scientific evidence relating to residues of the six hormones: (1) the EC has failed to put forward evidence demonstrating that residues of any of the six hormones in meat from cattle are greater than previously thought, or to assess the risk to consumers from exposure to residues of any of the hormones from cattle treated with the hormones for growth promotion purposes; and (2) JECFA's recent re-evaluation of the three naturally occurring hormones reached the same substantive conclusions as earlier evaluations.

(a) *The EC has failed to put forward evidence demonstrating that residues of any of the six hormones in meat from cattle are greater than previously thought, or to assess the risk to consumers from exposure to residues of any of the hormones from cattle treated with the hormones for growth promotion purposes*

90. The experts' responses indicate that the EC has failed to put forward evidence demonstrating that residues of any of the six hormones in meat from cattle are greater than previously thought or to assess the risk to consumers from exposure to residues of any of the hormones from cattle treated with the hormones for growth promotion purposes. Dr. Boisseau, citing to the EC's 1999 Opinion and its determination that no threshold exists for any of the hormones, notes that as a consequence of this conclusion the EC did not "conduct a quantitative assessment of the exposure of consumers to the residues of hormonal growth promoters including the determination of the levels of residues in food from treated animals."[187] In the absence of this evaluation, the EC was therefore unable to make any meaningful "comparison between these levels and the MRLs set up by Codex."[188] Dr. Boobis agrees that the EC failed to evaluate or assess actual residue levels in meat:

> In their 2002 Opinion, the Committee [*i.e.*, the EC's SCVPH] did not revisit exposure following use according to GVP. Rather, the Committee considered potential exposure following several inappropriate use scenarios. This was based on a series of experimental studies, to determine the consequences of a number of defined misuses on hormone levels in meat. However, whilst of potential value in any risk assessment, these data are limited in the absence of any information on the frequency of occurrence of such misuse in the use of the products in question in normal veterinary practice.[189]

[187] Dr. Boisseau Responses (Question 29), p. 18.

[188] Dr. Boisseau Responses (Question 29), p. 18.

[189] Dr. Boobis Responses (Question 30), p. 33.

Dr. Boobis provides a detailed critique of these "inappropriate use" studies, in which he concludes that, even in most of the extreme misuse scenarios developed by the EC, safe levels of hormone residues are not exceeded.[190]

91. Although Dr. De Brabander raises several hypothetical concerns regarding hormone residues in meat, his comments do not appear to be responsive to the Panel's inquiry as to whether the EC in fact evaluated evidence of residue levels in meat from cattle treated with any of the six hormones for growth promotion purposes in its Opinions nor do his responses cite to any such scientific evidence. Further, the concerns raised by Dr. De Brabander do not appear to be relevant to a discussion of the subject matter at hand, *i.e.*, residues in meat from cattle treated with any of the six hormones for growth promotion purposes. For instance, Dr. De Brabander opines that the earlier studies on residues are "old", they are "too much focused on the direct effect on human health", and the MRLs for the hormones "are high in relation to modern analytical limits (normally $\leq$ 1 µg/kg)" and "not acceptable."[191]

92. However, as noted by Dr. Boisseau, older data is neither irrelevant or "bad" data simply due to its age. Rather, it is the quality and quantity of data that is important,[192] and for the hormones at issue, a great deal of high quality data exists.[193] Further, the MRL for a veterinary drug is the maximum concentration of residue that is legally permitted or recognized as acceptable, based on the toxicological hazard for human health (expressed as the ADI).[194] Therefore, the statement by Dr. De Brabander that the MRLs for the hormones "are high in relation to modern analytical limits" is unexceptional; in fact, by definition the MRL for a drug residue should be higher than the analytical limit of detection.[195]

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[190] Dr. Boobis Responses (Question 62), pp. 50-52. *See* Section C(6) below for a detailed discussion of the misuse studies.

[191] Dr. De Brabander Responses (Question 29), p. 3.

[192] *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.")

[193] As explained in JECFA's Responses (at pp. 7-9), JECFA has specific and extensive requirements for the residue data that are used to derive MRLs. These requirements include information on the analytical method used to measure each residue and the performance factors of the method. Importantly, when comparing the 1988 and 1999 evaluations of residue studies for the hormones JECFA states, "[m]ost of the studies were the same. However, a few additional investigative studies were also reviewed. JECFA also performed a more detailed thorough review of the validity of the analytical methods used in the studies and only used data generated using valid methods." Therefore, Dr. De Brabander's statement that "from an analytical point of view these MRLs are unacceptable" is unfounded.

[194] Codex Responses (Question 9), p. 7.

[195] Note that the residue data used in the derivation of the MRLs in question were generated using valid analytical methods that were reviewed in detail by JECFA.

93. It appears that Dr. De Brabander is equating the goals for detection of illegal anabolic drugs in humans (doping) with detection of residues of veterinary drugs in food animals For the purpose of detecting illegal drugs (where the allowable concentration of the drug in question is zero), it is critical for the analytical method to accurately measure concentrations as close to zero as possible. For most veterinary drugs in food animals, the purpose of residue methods is not to detect any non-zero concentrations of the residue, but to determine if the residues exceed the finite concentrations that have been determined to be safe – in general, these levels do not approach zero and do not require ultra-sensitive methods as Dr. De Brabander suggests. Dr. Boisseau confirms this point:

> Nevertheless, it has to be reminded that, when MRLs have been established for a given substance, there is not any more a need for highly sensitive analytical methods but for a validated analytical method the sensitivity of which must be consistent with the values of the established MRLs. In addition, if it is true that ultrasensitive analytical methods remain useful to control the use of forbidden veterinary drugs, such as for example growth promoters in EU, they are less useful in the case of the three natural hormones, which are endogenously produced by food producing animals.[196]

As for actual hormone residue levels in meat, Dr. De Brabander does not present any evidence that hormone residue levels have been shown to be higher than previously thought, but rather speculates that "[t]he concentrations may seriously be underestimated."[197]

94. As to the earlier studies' focus on human health, analysis of the potential effect on human health is the logical endpoint for an evaluation of hormone residues that are to be consumed by humans. Dr. De Brabander indicates that these studies should instead have examined hormone excretions in cattle feces and urine.[198] Here, Dr. De Brabander is alluding to the possible environmental impact of the use of growth promoting hormones in cattle. This analysis is not germane to the question of whether meat and meat products from cattle treated with any of the hormones are safe for import and consumption; any of the hypothetical effects raised by Dr. De Brabander would presumably occur in the United States (where the cattle are actually located), rather than in export markets (where the cattle are not located).

95. Dr. De Brabander also provides anecdotal information relating to a testosterone sex spray as well as use of a substance called "ZMA" (a substance allegedly used by athletes) in his response. However, none of this information is responsive to the Panel's question, nor does it

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[196] Dr. Boisseau Responses (Question 32), p. 18.

[197] Dr. De Brabander Responses (Question 29), p. 3.

[198] Dr. De Brabander Responses (Questions 29 and 30), pp. 3-4. (*E.g.*, "[a]s demonstrated in several studies a major part of the hormones used are excreted through urine and faeces and the administration of natural hormones to a herd increases the concentration of these hormones in the environment." Note that the "environment" implicated in this statement would be the United States, where the herd resides; not the EC.)

provide evidence relating to hormone residue levels in meat from cattle treated with any of the six hormones for growth promotion purposes. For instance, the discussion of the androstenone (boar pheromone) spray neither provides any information regarding dose levels, nor is it relevant to the pathway at issue in the consumption of hormone residues in meat (*i.e.*, oral). ZMA is not one of the hormones at issue in this dispute, and the anecdotal discussion of its use by athletes does not appear to be relevant to a discussion of residues in meat from cattle treated with any of the six hormones for growth promotion purposes.

96. Dr. De Brabander concludes that, because humans already consume foods like meat and milk that contain estrogens which "don't give problems at a normal food consumption" that "just therefore there is no need to add more by artificial ways."[199] Yet, Dr. De Brabander provides no scientific discussion as to how the small additional amounts of any of the hormones found in meat from cattle treated for growth promotion purposes might pose any increased risk to consumers. Rather, his comment appears to be a personal opinion or policy statement rather than a scientific conclusion. Humans have consumed hormone residues in food for millenia without any evidence of an adverse health risk from those residues. Similarly, humans have consumed residues in meat from cattle treated with the six hormones for growth promotion purposes for decades without any evidence of a human health risk from these "additional" residues.[200]

(b) *JECFA's recent re-evaluation of the three naturally occurring hormones reached the same substantive conclusions as earlier evaluations*

97. The experts' responses confirm that JECFA's recent re-evaluation of the three naturally-occurring hormones reached the same conclusion as earlier evaluations, *i.e.*, that residues of the hormones in meat from cattle treated for growth promotion purposes are safe for consumers. The EC argues that JECFA's establishment of ADIs for the three natural hormones at its 52nd Meeting in 1999 marked a shift in its thinking regarding the safety of the hormones when used as growth promoters in meat.[201] The experts indicate that it did not. Dr. Boisseau notes "[i]f the

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[199] Dr. De Brabander Responses (Question 31), p. 5.

[200] *See*, *e.g.*, discussion of the experts on epidemiological studies relating to the use of hormones for growth promotion purposes in meat and the lack of a link to evidence of cancer at Section C(4)(b) above.

[201] The EC stresses in its answers to questions from the Panel after the first substantive meeting that: "However, as already explained the above-mentioned JECFA reports found that oestradiol 17β 'has genotoxic potential' and that the evidence for progesterone was interpreted 'on balance' as not having genotoxic potential. On the basis of these findings, JECFA did consider for the first time that ADIs were necessary to be fixed but not MRLs, because of the endogenous production of these natural hormones and the difficulties in applying the available detection methods in order to determine the origin of any residues in meat." EC Answers to Panel Questions, para. 129. *See also* EC Answers to Panel Questions, para. 97 (noting that JECFA's conclusion that estradiol 17β has "genotoxic potential" "led now, again for the first time, to propose the definition of an Acceptable Daily Intake (ADI) for oestradiol 17β, which was not the situation before.") The United States has addressed the argument that JECFA's determination that estradiol 17β has "genotoxic potential" in any way affected its decision making on that hormones. The experts have confirmed that it did not. *See* Section C(2)(b) above.

wording of the conclusions adopted by JECFA has been formally different, the substance of these conclusions remains unchanged," and that "[e]stablishing such ADIs had no specific implications as no MRLs have been established."[202] Further, "[t]hese new recommendations have not been considered by CCRVDF because CCRVDF did not request JECFA to reassess these hormones and because the new proposals of JECFA did not change the substance of the previous ones."[203]

98. Dr. Boobis comments that the re-evaluation of the hormones took into account "a number of additional studies on the toxicology and human (including epidemiological) evaluation of therapeutic exposures to the hormones (e.g. in the form of oral contraception or for hormone replacement therapy) that were not available in 1988."[204] These human therapeutic studies indicated that exposure to the hormones could have adverse effects on humans "albeit at levels appreciabl[y] higher tha[n] found in meat from treated cattle."[205] Establishment of an ADI would serve as a "benchmark for comparison with exposure via the diet."[206] Against that benchmark, a decision was made not to recommend an MRL due to the large margin of safety, and "CCRVDF endorsed the recommendation that MRLs for the natural hormones did not need to be specified."[207]

99. Dr. De Brabander is the lone expert to disagree with these conclusions, noting that JECFA's conclusion to set an ADI "is a recognition of the danger of hormones to human health and welfare in all of his [*sic*] aspects."[208] Dr. De Brabander does not provide any support for this statement, and does not clarify whether the "danger to human health . . . in all of [its] aspects" includes levels of the hormones found in residues in meat from cattle treated for growth promotion purposes. The responses of JECFA, Codex and the other two experts indicate that the

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[202] Dr. Boisseau Responses (Question 33), p. 19.

[203] Dr. Boisseau Responses (Question 33), p. 19. Codex confirms Dr. Boisseau's opinion. *See* Codex Responses (Question 18), p. 9.

[204] Dr. Boobis Responses (Question 33), p. 35.

[205] Dr. Boobis Responses (Question 33), p. 35.

[206] Dr. Boobis Responses (Question 33), p. 35.

[207] Dr. Boobis Responses (Question 33), p. 35. Indeed, on the basis of its detailed analysis, JECFA was able to conclude that MRLs were not necessary for the three natural hormones because residues in meat from cattle treated with the hormones for growth promotion purposes were equal to or less than 3% of the ADI in the case of estradiol 17β, and much less than 1% of the ADI in the case of progesterone and testosterone. *See* 52nd JECFA Report (2000), § 3.5, pp. 57-74. (Exhibit US-5).

[208] Dr. De Brabander Responses (Question 33), p. 8. The lack of agreement between Dr. De Brabander's response to the question of why JECFA set ADIs in 1999 and JECFA's justification for establishing these ADIs may indicate that Dr. De Brabander is not familiar with the international procedures used to evaluate the safety of residues of veterinary drugs in food animals.

decision to set an ADI is not evidence of such a danger.[209] Rather, the setting of an ADI permitted an evaluation of residue levels of the three hormones that could be ingested without any danger or risk to consumers.[210]

(c) *Conclusion*

100. The experts' responses indicate that the EC has failed to put forward any scientific evidence demonstrating that residues of any of the six hormones in meat are greater than previously thought, or assessed the risk related to the exposure of consumers to residues of any of the hormones in meat from cattle treated with the hormones for growth promotion purposes. These responses also confirm that JECFA's decision to set an ADI for the natural hormones did not mark a change in JECFA's or Codex's opinion as to the safety of the hormones when consumed as residues in meat from cattle treated for growth promotion purposes. Therefore, the EC has failed to base its permanent ban on estradiol 17β on a risk assessment within the meaning of Article 5.1 of the SPS Agreement and failed to take into account available scientific evidence within the meaning of Article 5.2 of the SPS Agreement. Further, the EC has failed to base its provisional ban on available pertinent information within the meaning of Article 5.7 of the SPS Agreement.

(6) Scientific evidence relating to good veterinary practices

101. The scientific evidence relating to good veterinary practices is relevant to the obligation in Article 5.1 of the SPS Agreement that Members must base their measures on a risk assessment, as appropriate to the circumstances, as well as Article 5.2's requirement that risk assessments take into account relevant processes and production methods, and relevant inspection, sampling and testing methods.[211] Further, an analysis of good veterinary practices is

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[209] *See* Codex Responses (Question 18), p. 9 ("In the case of estradiol-17 beta, progesterone and testosterone, they were re-evaluated by the 52nd JECFA (1999) at the initiative of the JECFA Secretariat. The 12th CCRVDF (2000), in recognising that it had not requested the re-evaluation of the three substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, decided to not consider the new recommendation of the 52nd JECFA.") (Emphasis added); JECFA Responses (Question 20), p. 18 ("Sufficient new data from observations in humans were available to the 52nd JECFA which were suitable to derive ADIs. The ADI not only provides an estimate of daily intakes which can be accepted over life time without appreciable health risks, it also enables a quantitative comparison of the excess intakes calculated on the basis of the above mentioned worst case scenario (see point 4 above). The Committee found that the excess intake was in the order of only 0.02 to 4% of the ADI depending on the substance and the product used for the treatment of the animals. Moreover, the establishment of an ADI implies that there is a threshold of effect for such a compound, below which now toxicological effects occur.") (Emphasis added).

[210] Indeed, Codex does not take action, or base public health standards, on ADIs, but rather only does so based on recommendations of MRLs.

[211] For purposes of evaluation of SPS measures under the SPS Agreement, the Appellate Body stated, "[w]e must stress . . . that Article 5 and Annex A of the SPS Agreement speak of 'risk assessment' only and *that the term 'risk management' is not to be found either in Article 5 or in any other provision of the SPS Agreement*."

relevant to Article 5.7 of the SPS Agreement and an analysis of whether the EC's provisional ban is based on available pertinent information. The issue of conditions of use is, however, perhaps best understood in the context of Article 5.6 of the SPS Agreement, which provides that a Member must ensure that its sanitary and phytosanitary measures are not more trade-restrictive than required to achieve its appropriate level of sanitary or phytosanitary protection. The fact that the EC has raised the issue of misuse[212] 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. The only health question then would be whether there are particular conditions of use under which there would be a health risk. If so, then the question becomes whether the EC's sanitary measures are more trade-restrictive than required to achieve the appropriate level of protection from that risk within the meaning of Article 5.6 of the SPS Agreement.

102. The responses from the experts indicate that: (1) the EC has failed to demonstrate that there is a risk to human health from the misuse of growth promoting hormones in the United States; and (2) the material put forward by the EC regarding misuse or abuse of the hormones at issue fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes.

Further, the Appellate Body concluded that misuse and the analysis of the potential for failure of controls are topics that are included in a "risk assessment" for purposes of the SPS Agreement:

> It should be recalled that Article 5.2 states that in the assessment of risks, Members shall take into account, in addition to "available scientific evidence", "relevant processes and production methods; [and] relevant inspection, sampling and testing methods". We note also that Article 8 requires Members to "observe the provisions of Annex C in the operation of control, inspection and approval procedures ...". The footnote in Annex C states that "control, inspection and approval procedures include, inter alia, procedures for sampling, testing and certification". We consider that this language is amply sufficient to authorize the taking into account of risks arising from failure to comply with the requirements of good veterinary practice in the administration of hormones for growth promotion purposes, as well as risks arising from difficulties of control, inspection and enforcement of the requirements of good veterinary practice.
> . . . . .
> We disagree with the Panel's suggestion that exclusion of risks resulting from the combination of potential abuse and difficulties of control is justified by distinguishing between "risk assessment" and "risk management". As earlier noted, the concept of "risk management" is not mentioned in any provision of the SPS Agreement and, as such, cannot be used to sustain a more restrictive interpretation of "risk assessment" than is justified by the actual terms of Article 5.2, Article 8 and Annex C of the SPS Agreement. The question that arises, therefore, is whether the European Communities did, in fact, submit a risk assessment demonstrating and evaluating the existence and level of risk arising in the present case from abusive use of hormones and the difficulties of control of the administration of hormones for growth promotion purposes, within the United States and Canada as exporting countries, and at the frontiers of the European Communities as an importing country.

EC – Measures Concerning Meat and Meat Products (Hormones), Appellate Body Report adopted on 13 February 1998, WT/DS26/AB/R ("Hormones" or "EC - Hormones"), paras. 181; 205-207.

[212] *See*, *e.g.*, EC Answers to Questions from the Panel, para. 91.

(a) *The EC has failed to demonstrate that there is a risk to human health from the misuse of growth promoting hormones in the United States*

103. While there is some disagreement among the experts as to the extent to which the EC has assessed a risk to human health from the misuse of growth promoting hormones in the United States, a close examination of the experts' responses indicates that the EC has not demonstrated that such a risk exists. Dr. Boisseau notes that "as the [EC] did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the scientific evidence referred to by the [EC] assesses the risk to human health from residues resulting from these misuses/abuses."[213] Dr. Boobis agrees, stating: "[t]here was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies. Indeed, the SCVPH (2002) simply noted that '[t]herefore, these data have to be considered in any quantitative exposure assessment exercise', without undertaking such an exercise."[214]

104. Dr. De Brabander appears to disagree with Drs. Boobis and Boisseau, but his responses fail to address the actual questions posed by the Panel, and in certain instances his opinions are simply based on anecdotal information and policy considerations rather than scientific evidence or citations to the EC's purported risk assessments. For example, in response to the Panel's inquiry as to whether the EC assessed the risk from misplaced implants (Question 48), Dr. De Brabander simply notes, "any control mechanism, that is only based on audits and paper work will not prevent farmers to use either uncorrect use of legal production aids either [*sic*] illegal growth promoters which are readily available in the U.S. and Canada through the internet." Dr. De Brabander fails to substantiate this statement, which appears to be purely conjectural; he does not provide any evidence of failure of controls in the United States, nor does he cite to any portions of the EC's purported risk assessment where the EC actually evaluated the risk of failure of controls or misuse. In any event, no measure, be it a ban or a system of controls, can ever be relied upon to "prevent" an occurrence entirely. This is evidenced by the fact that, despite imposing a ban on the use of growth promoting hormones, the EC has been unable to "prevent" their sale and use in the black market.[215]

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

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

[215] *See* U.S. Rebuttal Submission, paras. 64-65, *citing*, *e.g.*, Stephany, *Hormones in meat: different approaches in the EU and in the USA*, APMIS 109, p. S 357 (2001) ("It has to be concluded that in some EU Member States an exten[d]ed black market exists. For the USA, no experimental evidence is available for such a black market.") (Exhibit US-29).

105. As explained by the United States in its Rebuttal Submission, the U.S. system of controls is not a simple matter of audits and paper work.[216] The United States, through cooperation between the Food Safety and Inspection Service ("FSIS") of the United States Department of Agriculture ("USDA") and the FDA, has rigorous programs in place which provide efficient safeguards against the hypothetical failure of controls in the production of meat and meat products. These programs 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 addition to regulation at the federal level, many states and even individual feedlots have Beef Quality Assurance Programs which set high standards for beef management practices to maximize the quality and safety of beef.[217] Key components of these programs include proper training of feedlot employees and managers to ensure that management practices do not lead to violative residues or quality defects.

106. All growth promoting implants are clearly labeled for subcutaneous placement in the middle third of the ear, and the ears of all cattle are removed at slaughter and discarded. Any evidence at the time of slaughter of improper use of growth promoting implants, which the EC claims is common practice in the United States but provides no data to support, will result in condemnation of the carcass by FSIS inspectors and significant economic loss to the producer. Therefore, speculation by the EC about the effects of consumers eating whole implants, implant sites, or meat from over-dosed cattle[218] are paper exercises at best which ignore U.S. inspection practices and evidence of decades of experience with the safe use of these products. Clearly, the U.S. beef production system has numerous controls in place at multiple levels (federal, state and feedlot) which effectively mitigate the risk to human health from the misuse of growth promoting hormones in cattle.

107. Dr. De Brabander cites to two pieces of evidence in support of his conclusion that the U.S. system of controls does not work or is subject to failure, neither of which appears to be convincing or germane to the debate of whether or not the EC has indeed evaluated the likelihood of this occurrence. He notes that "[t]wo years ago we had some american students in veterinary medicine in an exchange program; their knowledge of 'hormones' their use in the USA and the risks involved was almost zero."[219] At best this statement is anecdotal evidence, and it certainly cannot be extrapolated to the broader conclusion that controls are likely to fail in the United States. Dr. De Brabander also cites to a controlled study conducted by scientists at

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[216] *See* U.S. Rebuttal Submission, paras. 54-66.

[217] Examples of Beef Quality Assurance Programs in Ohio, Minnesota and Iowa can be found at http://www.ag.ohio-state.edu/~obqa/; http://www.mnbeef.org/bqa/BQA_Manual/Introduction.htm; and http://www.iabeef.org/BQA/Default.aspx.

[218] *See*, *e.g.*, EC 1999 Opinion, §§ 3.3.1, 3.3.2 (pp. 30-31) (Exhibit US-4).

[219] Dr. De Brabander Responses (Question 44), p. 13.

the University of California-Davis using Zilpaterol (a beta-agonist not approved by the FDA for commercial use in the United States) and Revalor (trade name for an FDA-approved growth promoting implant containing estradiol 17β and trenbolone acetate) in cattle as evidence "illustrat[ing] that farmers (and vets) have indeed economic incentives to misuse growth promoting substances."[220] The Zilpaterol study does not support this conclusion, nor does it document or endorse the commercial use of Zilpaterol. Rather, it is simply an example of a single research study, conducted under controlled conditions on a limited number of animals, in which scientists investigated the combined effects of two treatments on growth performance in cattle. Nothing in the Zilpaterol study speaks to the potential of failure of controls or misuse of growth promoting hormones in the United States.[221]

(b) *The material put forward by the EC regarding misuse or abuse of the hormones at issue fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes*

108. The experts' responses confirm that the material put forward by the EC regarding misuse or abuse of any of the six hormones fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes. Dr. Boisseau reiterates that JECFA does not perform an evaluation of the potential for misuse,[222] and notes that "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."[223]

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[220] Dr. De Brabander Responses (Question 45), p. 14.

[221] In the United States, unapproved drugs such as Zilpaterol are regulated as "new animal drugs for investigational use." As stated in 21 CFR § 511.1, "[e]dible products of investigational animals in clinical trials are not to be used for food." Similarly, Dr. De Brabander's discussion of hormones used by body builders and athletes is irrelevant to a discussion of the use of growth promoting hormones in cattle according to good veterinary practices. *See* Dr. De Brabander Responses (Question 47), p. 15.

[222] Risk assessments performed by JECFA, the EC's European Medicines Agency ("EMEA") and the FDA evaluate the use of veterinary drugs assuming that the drugs are administered according to good veterinary practices. Were this not the case, it would be impossible to develop international food safety standards, *i.e.*, there would be no benchmark against which safety evaluations could be conducted. Further, it is important to note that any veterinary drug could be misused. If regulatory authorities based their evaluations against a misuse standard, then there would be virtually no approvals of veterinary medicines. The evidence is clear that there are a large number of veterinary drugs on the market in both the United States and the EC which were approved assuming that they would be administered according to good veterinary practices, indicating that this is the norm for such evaluations. It is curious that the EC has not used this standard in its evaluation of the six hormones at issue in this dispute, assuming instead extreme misuse scenarios for each hormone.

[223] Dr. Boisseau Responses (Question 51), p. 25.

109. Dr. Boobis agrees that the EC has made "no attempt to evaluate the risks"[224] from misuse, either in its Opinions or in underlying studies. Accordingly, the EC has not presented any materials that cast doubt on the JECFA or Codex evaluation of the safety of the hormones. In support of this conclusion, Dr. Boobis engages in an extensive analysis of the additional studies commissioned and cited by the EC since 1997.[225] He cites to several studies analyzed earlier by the United States in its Rebuttal Submission, and reaches similar conclusions regarding their results:

1. Lange *et al*., *Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: effect of the implant preparations Filaplix-H, Raglo, Synovex-H and Synovex Plus*.

"In study 5, the impact of misuse and multiple dosing on residual hormone levels in meat was determined. Dosing at up to 10 times the approved dose, resulted in an increase in the tissue concentrations of some hormones in some tissues to value above the MRL for those hormones for which Codex has established an MRL."[226]

"'Treatment with zeranol and testosterone propionate, even after multiple application, does not cause any problems, as far as infringement of threshold levels is concerned.'"[227]

"For oestradiol, the maximum increase observed in any tissue was not greater than proportional to the dose applied. Hence, even at 10-fold the approved dose, intake would be well below the ADI. This would be offset by the fact that not all tissues had such elevated levels, and the probability of consuming such high residue levels of a regular basis is minimal. It should also be noted that Codex did not specify an MRL for oestradiol, as it was considered unnecessary."[228]

2. Daxenberger *et al*., *Detection of anabolic residues in misplaced implantation sites in cattle*.

"In the study on misplaced implantation sites (Daxenberger et al, 2000), substantial residual hormone was sometimes found at the implantation site when this was not as recommended. However, for these findings to have significance for the consumer a number of factors need to be considered. These include the likelihood of off-label use of the hormones, the

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[224] Dr. Boobis Responses (Question 48), p. 42.

[225] *See* Dr. Boobis Responses (Question 62), pp. 50-52 ("Multiple implanting, multiple dosing").

[226] Dr. Boobis Responses (Question 62), p. 50. (Emphasis added).

[227] Dr. Boobis Responses (Question 62), p. 50. (Emphasis added).

[228] Dr. Boobis Responses (Question 62), p. 50. (Emphasis added).

failure to detect the implantation site, the use of the implantation site for food use, the contribution of the contaminated meat to the diet and the frequency of such contamination. No data have been presented on the prevalence of such significant contamination as a consequence of the veterinary use of the hormones. Indeed, no evidence is presented that such misuse does occur with the consequences suggested by the authors."[229]

3. Daxenberger *et al*., *Detection of melengestrol acetate residues in plasma and edible tissues of heifers*.

"In studies on MGA (Daxenberger et al, 1999) tissue levels increased with dose, most markedly in fat. Whilst in fat, there was a roughly proportional increase with dose, in other tissues (muscle, kidney, liver) the fold-increase was appreciably less than the fold-increase in dose. Using the values obtained in the study of Daxenberger et al (1999) at 10 times the maximum approved dose, consumption of all four tissues (liver, kidney, fat and muscle) at the JECFA levels (300 g muscle, 100 g liver, 50 g kidney and 50 g fat per day) would result in a slight exceedance of the ADI (2.5 µg cf 1.8 µg). However, it should be noted that this would require all of the tissues to be from animals treated with the high dose, and exposure would have to be over a prolonged period of time. The probability that this would occur is extremely low."[230]

110. In summary, Dr. Boobis notes the following regarding the EC's research, including the 17 Studies:

> 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.[231]

111. Dr. De Brabander disagrees, noting that the materials put forward by the EC "call[ ] indeed into question" the applicability of Codex standards. However, Dr. De Brabander presents no scientific evidence in support of this conclusion. Dr. De Brabander cites to the "older" experiments on which JECFA relied in setting ADIs for the hormones, but fails to provide any

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[229] Dr. Boobis Responses (Question 62), pp. 50-51. (Emphasis added).

[230] Dr. Boobis Responses (Question 62), p. 51. (Emphasis added).

[231] Dr. Boobis Responses (Question 62), p. 58. (Emphasis added).

context for this concern by noting any "newer" material that would support the conclusion that the "old" evidence is no longer relevant.[232] Perhaps of greatest interest, Dr. De Brabander does not find support for his conclusion in the numerous studies produced by the EC in which extreme misuse scenarios were created and contemplated. As noted by the United States in its Rebuttal Submission, and confirmed by Dr. Boobis' analysis above, even in the artificial scenarios developed by EC scientists, in most cases extreme misuse and overdosing of cattle with implants did not result in violative residue levels, *i.e.*, levels exceeding ADIs and MRLs.[233] In addition, Dr. De Brabander cites to concerns of animal welfare and impact on the environment, neither of which has been argued by the EC in the course of these proceedings. Finally, Dr. De Brabander claims that "most consumers aren't prepared to take this risk."[234] Dr. De Brabander cites to no scientific evidence in support of this conclusion, which appears to be little more than a personal opinion or policy statement.

(c) *Conclusion*

112. The experts' responses, insofar as they are based on the scientific evidence relating to good veterinary practices and misuse, confirm that the EC has failed to demonstrate that there is a risk to human health from the misuse of growth promoting hormones in the United States and that the material put forward by the EC regarding misuse or abuse of the hormones at issue fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes. Therefore, the experts' responses demonstrate that the EC has failed to base its import ban on meat from cattle treated with estradiol 17β on a risk assessment, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement, and has similarly failed to satisfy Article 5.2's requirement that a risk assessment take into account relevant processes and production methods and relevant inspection, sampling and testing methods. In addition, the experts' responses demonstrate that the EC has not satisfied its obligation under Article 5.7 of the SPS Agreement to base a provisional ban on available pertinent information. Finally, the experts' responses confirm that the EC, by imposing an import ban (whether permanent or temporary) on imports of 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.

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[232] *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.")

[233] *See* U.S. Rebuttal Submission, paras. 54-66.

[234] Dr. De Brabander Responses (Question 51), p. 18.

D. Conclusion

113. It is natural that in six sets of separate responses from the experts and three sets of responses from international organizations there would be some differences in the responses provided. However, upon analysis of their responses and evaluation of the scientific evidence cited therein, it is apparent that there are substantial areas of agreement amongst the experts. As demonstrated above, their responses are consistent with the following conclusions:

(1) There are certain necessary components or elements of a risk assessment, and the EC has failed to satisfy each of those elements in the Opinions upon which it based its permanent ban on estradiol 17β.

(2) The scientific evidence does not support the conclusion that any carcinogenic effects of estradiol 17β are related to a mechanism other than hormonal activity.

(3) The scientific evidence does not support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones.

(4) The scientific evidence does not demonstrate that estradiol 17β will have carcinogenic or tumorigenic effects at concentrations found in residues in meat from cattle treated with hormones for growth promotion purposes.

(5) The scientific evidence and information relating to the five provisionally-banned hormones is sufficient to conduct an assessment of the risks to human health from consumption of meat from cattle treated with any of the five hormones for growth promotion purposes.

(6) The scientific evidence cited by the EC in its Opinions does not demonstrate that any of the five provisionally-banned hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity.

(7) The scientific materials produced and cited by the EC (including the "17 Studies") have not identified any gaps or insufficiencies in the scientific evidence such that more study is necessary before the risk from consumption of meat from cattle treated with the five provisionally-banned hormones for growth promotion purposes can be assessed.

(8) Each of the hormones has been used for growth promotion purposes in cattle and evaluated for a sufficient period of time with no evidence of adverse effects to adequately address any concern regarding long latency periods of cancer.

(9) Epidemiological studies cited by the EC do not identify a link between cancer and residues of the six hormones in meat from cattle treated with the hormones for growth promotion purposes.

(10) The EC has failed to demonstrate that meat from cattle treated with hormones for growth promotion purposes poses a risk to sensitive populations.

(11) The EC has failed to demonstrate "other risks" to human health from consumption of residues of the hormones in meat from cattle treated for growth promotion purposes, such as effects on the immune system.

(12) The EC has failed to put forward evidence regarding or assessed the risk related to the exposure of consumers to residues of any of the six hormones in meat from cattle treated with the hormones for growth promotion purposes.

(13) JECFA's decision to set an ADI for the natural hormones did not mark a change in JECFA's or Codex's conclusions as to the safety of the hormones when consumed as residues in meat from cattle treated for growth promotion purposes.

(14) The EC has failed to demonstrate that there is a risk to human health from the misuse of growth promoting hormones in the United States.

(15) The material put forward by the EC regarding misuse or abuse of the hormones at issue fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes.