

**United States – Continued Suspension of Obligations in the  
EC – Hormones Dispute**

**Comments of the United States on the EC’s Replies to Questions  
from the Panel after the Second Substantive Meeting**

**October 31, 2006**

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

**A. Questions to all the Parties:**

Q1. *With reference to the statement by the European Communities, inter alia in para. 12 of the EC reply to Question 3 of the United States, do the parties consider that a Panel is entitled to address “systemic claims” or issues related to “systemic obligations” and, if so, to what extent?*

2. The EC’s response to Question 1 reemphasizes several points raised in the U.S. response to this question. In our response, we explained how what the EC refers to as EC’s “systemic claims” are premised on the EC’s view of how the *Understanding on Rules and Procedures Governing the Settlement of Disputes* (“DSU”) should be rewritten rather than grounded in the actual text of the DSU. The EC’s response highlights this fact. For example, the EC argues that “from the EC’s point of view, the continued application of sanctions in the face of presumed compliance and in the absence of a compliance review constitutes a violation of a procedural nature, irrespective of the substantive requirements of actual compliance.” (Emphasis added). This statement is remarkable for several reasons.

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

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

Q4. *Has the European Communities assessed in a systematic manner the existence and level of risks from failure to observe good veterinary practices with respect to the administration of oestradiol 17β as a growth promoting hormone to cattle, in particular in the United States’ and Canada’s markets? If so, please indicate where this assessment is to be found in the evidence provided to the Panel.*

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

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

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

8. Indeed, none of the experts (including Dr. De Brabander) pointed to any evidence presented by the EC of an actual risk from the misuse of the six hormones as growth promoters

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<sup>1</sup> See, e.g., U.S. Rebuttal Submission, paras. 6-8, 15-16.

<sup>2</sup> See, e.g., U.S. Rebuttal Submission, Section II.B.4.

<sup>3</sup> See Response of Dr. Boobis to Panel Question 62.

in cattle in the United States. Nor did any of the experts opine that the EC had actually assessed in a proper manner the likelihood that such a failure would occur.<sup>4</sup>

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

10. For instance, the EC’s arguments relating to the existence of a risk of multiple dosing, or stacking of implants are misguided. The EC argues that there are economic incentives to misuse growth promoting hormones (*i.e.*, not abide by on-label instructions).<sup>6</sup> However, no such incentives exist, as individual implants are marketed to provide optimal doses.<sup>7</sup> The EC’s purported “evidence” of the risk for stacking of implants is the University of Nebraska Beef Cattle Update (Exhibit US-27), cited extensively in Exhibit EC-73.<sup>8</sup> However, as noted by the Update’s author, Dr. Dee Griffin, the Nebraska Beef Cattle Update does not support the conclusion that stacking of implants is either a common or recommended practice in the United States. To the contrary, Dr. Griffin notes:

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

11. In other words, according to Dr. Griffin, “[u]se of FDA approved growth promotants other than as labeled is a costly mistake.” This is why “beef production specialists in the USA never recommend simultaneous or double implant administration.”<sup>9</sup> The EC also notes (in its answer to Question 12) that “multiple implanting of animals with these hormones is recommended by the manufacturers.” However, the EC provides no evidence to support this

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<sup>4</sup> See U.S. Response to Panel Question 4 after the Second Substantive Meeting.

<sup>5</sup> See, e.g., U.S. Rebuttal Submission, Section II.B.4; U.S. Comments on Responses of the Experts, paras. 101-112.

<sup>6</sup> See, e.g., Exhibit EC-73, para. 22.

<sup>7</sup> See Letter from Dr. Dee Griffin (Exhibit US-28).

<sup>8</sup> Exhibit EC-73, paras. 22 (fn. 35) and 47 (fn. 63), and fn. 37.

<sup>9</sup> Exhibit US-28 (emphasis added).

statement. To the contrary, FDA approval of veterinary drugs includes the regulation of manufacturers' labels and none of the labels for the growth promoting hormones at issue recommend treatment with more than one implant at a time.<sup>10</sup>

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

13. For example, upon discovery of the illegal use of growth promoting hormones in the veal industry, the United States Department of Agriculture's Food Safety and Inspection Service (“FSIS”) published Notice 31-04: *Verification of implant usage in non-ruminating calves (i.e., veal calves), providing instructions for inspection program personnel to use when they suspect the use of implants in non-ruminating calves*. This direction to field personnel made clear that any non-ruminating (veal) calf presented for slaughter with an implant or on which there is evidence of implant use was to be condemned by USDA inspectors. USDA inspectors visually inspect veal calves (and feedlot cattle) for any signs of implant use during ante-mortem (pre-slaughter) and post-mortem (post-slaughter) inspection.

14. Additionally, on 16 July 2004, the U.S. Food and Drug Administration (“FDA”) and FSIS jointly issued a letter to the American Veal Industry, as well as to other trade associations, reiterating that the practice of implanting food animals that are to be marked as “veal” with growth promoting implants is illegal. Finally, in order to ensure that veal illegally treated with

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<sup>10</sup> For example, the manufacturer's label for Synovex Plus implants (estradiol plus trenbolone acetate; [http://www.wyeth.com/products?product=/wyeth\\_html/home/products/animal\\_health/SYNOVEX%e2%ae%20Implants/prescribinginfo.html](http://www.wyeth.com/products?product=/wyeth_html/home/products/animal_health/SYNOVEX%e2%ae%20Implants/prescribinginfo.html)) states “DOSAGE: One implant (eight pellets), containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate, is administered to each steer or heifer by subcutaneous implantation in the middle one-third of the ear” and “DIRECTIONS: Implant complete contents of one cartridge cell per steer or heifer.”

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

<sup>12</sup> See EC Responses to Questions from the Panel After the Second Substantive Meeting, Question 4, paras. 15-16 and footnotes 4-5.

growth promoting hormones was not entering the U.S. market or exported, FSIS included the testing of veal in its National Residue Program. There have been no positive samples found in either 2004 or 2005, a fact that is clear evidence of the effectiveness of FSIS/FDA's efforts to eradicate illegal use of hormones in this industry.

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

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

Q5. *In its comments on comments of the United States and Canada on experts replies to the Panel questions (in particular Question 13), the European Communities indicates that oestradiol 17 $\beta$  might be a “weak genotoxin” (para. 44). At what doses is genotoxicity observable in vivo? How are these doses comparable to those found in meat from cattle treated with growth promoting hormones? How would this assertion affect the identification of adverse effects and the evaluation of potential occurrence of these effects from consumption of meat from cattle treated with oestradiol 17 $\beta$  for growth promotion purposes?*

17. In an attempt to justify the dosage of estradiol administered to rats in the study by Cavalieri *et al.* (Exhibit EC-125) as “not massively high”, the EC notes in its response to Question 5 the imminent publication of an underlying study (Mailander *et al.*) which would

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

**B. Questions to the European Communities:**

Q6. *Should the Panel agree with the European Communities' main claim that the United States and Canada have breached Article 23 of DSU read together with Articles 21.5 and 22.8, what would be the consequences of such a conclusion for the United States and Canada? More particularly, would the United States and Canada:*

- (a) be expected to withdraw the suspensions of concessions or other obligations or suspend their application?*
- (b) be expected to initiate an Article 21.5 procedure against the EC? or*
- (c) would they be expected to do both?*

*(Please note that the Panel is fully aware of its obligations under Article 19 DSU)*

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

19. Consequently, the EC's response to Question 6 is rather revealing. First, the EC response is a telling snapshot of its overall failure to demonstrate that the United States has breached its obligations under the DSU by continuing to suspend concessions to the EC despite the EC's unilateral declaration of compliance. As a general matter, if the U.S. suspension of concessions were a measure in breach of its WTO obligations, the United States would not be able to maintain them. However, the EC's reply indicates that the United States would be free to

continue to apply the suspension of concessions and related obligations pending the outcome of an Article 21.5 proceeding.<sup>13</sup> The EC thus admits that even under its own theory, the U.S. suspension of concessions is not inconsistent with the DSU. Furthermore, the EC thus admits that the suspension of concessions is not related to any “new” determination by the United States, in breach of Article 23 of the DSU, that the EC measures taken to comply are inconsistent with the covered agreements.

20. Second, the EC’s reply confirms that the United States is not in breach of Article 21.5 of the DSU. For example, the EC argues that “there can be no doubt that the United States and Canada are under an obligation to withdraw the suspension of concessions . . . if they do not initiate a 21.5 proceeding.” However, to date, the EC has failed to identify any specific obligation in the text of Article 21.5 that has allegedly been breached by the United States. The United States has noted this failure on several occasions.<sup>14</sup> It is therefore remarkable that the EC avers that “there can be no doubt that [the United States] [is] under an obligation to initiate a 21.5 proceeding.” Rather than finding a basis for its claim in the text of Article 21.5, the EC’s claim of a U.S. breach is simply a product of its so-called “systemic” claims of a breach of the DSU which find no basis in the actual text of the DSU.<sup>15</sup>

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

Q8. *The Panel understands that the European Communities initiated risk assessments with respect to all six hormones at issue (see, e.g., Directive 2003/74/EC, third introductory paragraph).*

- (a) *Could the European Communities confirm, with respect to oestradiol 17  $\beta$  and in light of its statement in para. 192 of its rebuttal and its comments on Question 14 of the Panel to the experts, whether:*
  - (i) *it proceeded through the four steps of risk assessment identified by Codex;*  
*or*
  - (ii) *could have proceeded through the four steps but decided not to do so in light of its findings on genotoxicity of oestradiol 17  $\beta$ ?*

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<sup>13</sup> See EC Responses to Questions from the Panel After the Second Substantive Meeting (Question 4), paras. 15-16.

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

<sup>15</sup> See U.S. First Written Submission, Section IV.D.3(a)(iii); U.S. Answers to Panel Questions after the First Substantive Meeting, paras. 11, 16-17, 38-40; U.S. Rebuttal Submission, paras. 5-12.

- (b) *Could the European Communities confirm, with respect to each of the other five hormones at issue, at what stage(s) of its risk assessment it considered that relevant scientific evidence was insufficient and decided to provisionally ban the importation of meat treated with those hormones on the basis of available pertinent information.*

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

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

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

25. Second, the EC’s exposure calculations rely on results of the Klein assay (1994), which indicated that blood levels of estradiol in prepubertal boys were 100-fold lower than previously reported. The United States has demonstrated the flaws of the Klein assay on several occasions<sup>19</sup>

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

<sup>17</sup> U.S. Comments on the Responses of the Scientific Experts, paras. 18-32; *see also* U.S. Oral Statement (Expert Issues) at the Second Substantive Meeting, paras. 18-20.

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

<sup>19</sup> *See, e.g.*, U.S. First Written Submission, paras. 84 (and footnote 92) and 159; U.S. Rebuttal Submission, para. 44.



and the validity of this assay was discussed in detail at the meeting with the experts. While there seemed to be general agreement among the experts that blood levels of estradiol in prepubertal children may be lower than previously believed, the EC has not established the magnitude of the difference, and there was certainly no agreement among the experts on the 100-fold difference cited by the EC. The EC itself recognized the inaccuracy of the Klein assay results in its Comments on the Replies by the Panel Experts (Question 38).<sup>20</sup> Equally as speculative in the EC's exposure calculation is the assumption that the metabolic clearance rate of estradiol in children is one-half that of adults. No scientific data have been presented to support this assumption.

26. Third, the EC's exposure calculations are flawed because they use U.S.-permitted incremental increases<sup>21</sup> to estimate actual daily exposure to estradiol from eating beef. These permitted incremental increases are levels of residues that are permitted in excess of increments above the concentrations of estradiol naturally present in untreated animals; they do not represent actual amounts of estradiol found in edible tissues. Therefore, use of these numbers to derive an "acceptable daily intake" of 102 ng/person/day is factually incorrect. As the United States has stated previously, a more accurate (and still very conservative) estimate of excess daily intake of total estrogens from eating beef from treated animals – 30-50 ng/person/day, *i.e.*, one third to one half of the EC's erroneous estimate of 102 ng/person/day – can be found in the residue monograph from the 52nd JECFA meeting.<sup>22</sup>

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

Q9. *Can the European Communities explain the meaning it gives to the term "mere doubt" in para. 181 of the EC second submission (US case)?*

28. In its response to Question 9, the EC defines "mere doubt" as "not any kind of doubt but doubt that is scientifically established." The United States has not been able to locate, let alone find a definition of, the term "mere doubt" in any scientific materials, the SPS Agreement, or

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

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

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

WTO dispute panel or Appellate Body guidance. The EC appears to have invented this term during the course of these proceedings, and now hopes to have its measures analyzed against the backdrop of this fictitious (and self-defined) standard. This is an untenable position and should be disregarded as such. In any event, pursuant to the EC's own definition, a "mere doubt" must be a "scientifically justified" doubt. The EC has failed to present any evidence that there is scientifically-justified doubt about the safety of any of the six hormones when used for growth promotion purposes in cattle. Therefore, the EC has failed to satisfy its own standard.

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

29. In its response to Question 11, the EC states that "[i]t is scientifically not disputed (in this case even by the defending parties) that life-time exposure of humans to the levels of endogenous production of oestrogen (and in particular to oestradiol-17 $\beta$  and its metabolites) and, most likely, to the other two natural hormones (testosterone and progesterone) are sufficient to cause and/or promote cancer in some individuals." To the contrary, in the course of these proceedings the United States has never argued that endogenous hormones can cause or promote cancer. Nor has the EC presented any convincing evidence that this is so. It is overly simplistic and unscientific to say that endogenous hormones are "sufficient" to cause cancer, and the EC's response to Question 11 appears to be nothing more than an attempt to attribute statements to the United States and Canada that they have never made. Furthermore, the EC has failed to present evidence that there is any "additive" risk from the consumption of meat from cattle treated with any of the six hormones for growth promotion purposes.

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

31. Rather than citing to Exhibits EC-34 and 51A (some of the EC's more recent data that show a small and in certain cases undetectable increase in residue levels), the EC refers instead to Table 2 of its 1999 Opinion in its attempt to show that the residue level increase is "substantial." However, some of the data in Table 2 refer to veal calves and bulls, neither of

which are relevant to this dispute.<sup>23</sup> Further, neither the source nor the date of these data is indicated in Table 2. It is therefore not possible to evaluate the validity of these data or, more importantly, whether they accurately represent the average increase in estradiol residues in treated cattle (versus the most extreme cases).

Q12. *A 1999 Report of the Committee for Veterinary Medicinal Products of the European Communities refers to the low bioavailability of oestradiol 17β. How is this finding reconciled with references to bioavailability in the SCVPH Opinion? (please refer to comments by the parties on the Panel's Question 43 to experts)*

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

33. In addition, the EC states that JECFA, and by extension the 1999 CVMP Opinion, considered “only some of the residues of oestradiol-17β in meat; in particular, they have not considered the lipoidal (fatty acid) esters- nor estrone residues.” This statement is, at least in part, factually incorrect. The residue monograph of the 52nd JECFA Meeting contains 23 tables describing concentrations of estrone in edible tissues from both untreated and treated cattle.

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

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

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

Theoretical daily intakes were calculated and clearly presented for estrone alone, estradiol alone, and estrone and estradiol together (“total estrogens”).

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

Q16. *Please explain the reason for the differences between the “list of the 17 studies” that was appended to the 2002 Opinion and the one that was provided to the Panel. (please see paragraph 20 of the United States’ Rebuttal Submission and its Table 1)*

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

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