

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

**Responses of the United States to Questions from the
European Communities after the Second Substantive Meeting**

October 18, 2006

A. EC Questions to the United States and Canada:

Q1. *Please explain, if possible in detail, what kind of scientific evidence on exposure-assessment from residues in meat treated with the six hormones for animal growth promotion was used by the United States and Canada when these substances were authorised? Was this exposure assessment a quantitative one? Please provide concrete reference to studies used in your exposure assessment and, if possible, to those of JECFA for the six hormones in question (in case you know the references).*

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

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

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

4. For each of the three synthetic hormones, sponsors also performed extensive toxicological testing in experimental animals² to determine the dose at which the hormone produced an adverse effect and the dose at which no effect was observed (no effect level or “NOEL”). The NOEL of the most sensitive toxicological effect (*e.g.*, reproductive, developmental, tumorigenic) in the most sensitive species examined (*e.g.*, rat, mouse, rabbit) was

¹ <http://www.fda.gov/cvm/Guidance/published.htm>, Guidance 3

² This testing is also explained in FDA Guidance 3.

then divided by an appropriate safety factor to determine an acceptable daily intake (“ADI”). The ADI was then used to calculate a safe concentration for each edible tissue from cattle as follows: safe concentration = ADI × 60 kilograms (weight of average person) ÷ grams consumed per day. The food consumption factors currently used by FDA are: muscle, 300 grams; liver, 100 grams; fat and kidney, 50 grams each.³ FDA determined that for each of the synthetic hormones, the total residues (*i.e.*, residues of toxicological concern) were less than those calculated from the respective ADI. Therefore, FDA concluded that consumption of these residues in edible tissues from treated cattle does not pose a risk to human health.

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

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

Q2. *Please indicate, if possible in detail, whether your risk assessments, and if you know those of JECFA, of the six hormones in question for animal growth promotion have attempted to calculate the risk to humans from the additional exposure resulting from the residues in hormone-treated meat when used according to GVP and when GVP is not respected. Was it a quantitative exposure assessment? If so, please provide the precise reference to the data. (Please note that we are not referring here to residue-depletion studies contained in CAN Exhibit-17, since the EC has also conducted such residues depletion studies for its 1999-2002 risk assessments).*

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

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

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

8. That being said, we are happy to provide more information for background, although we note that this is the sort of question that the EC could have posed earlier to better inform its own risk assessment. As explained in the FDA Guidance⁵ referenced in the response to Question 1, FDA requires that total residue depletion studies be conducted using the dose that is the highest intended treatment level and that these studies should model the exposure received by the target animal. In the case of the six hormones in question, the highest intended treatment level was (and still is) one implant per animal, consistent with good veterinary practice.

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

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

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

⁵ <http://www.fda.gov/cvm/Guidance/published.htm>

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

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

Q3. *The EC understands that some of the experts (Drs. Guttenplan, Sippel and Cogliano) have stated that it is not possible to determine with accuracy the dose-response curve at the very low levels of exposure from these hormones in general and when used for animal growth promotion. Do you agree with these statements? If not, could you please provide the precise references to scientific studies where this has been done? What would be the implications of this impossibility for the need to perform a quantitative or qualitative exposure assessment for these hormones when used for animal growth promotion?*

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

14. Dr. Guttenplan concluded that there is no risk for carcinogenicity below the acceptable daily intake level ("ADI") for estradiol at the meeting with the experts, thereby indicating that any carcinogenic effects would be a result of doses above the threshold (levels exponentially greater than those found in residues in meat from treated cattle). Dr. Boisseau noted that "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of oestradiol-17 β are related to a mechanism other than hormonal activity."⁸ As noted by Dr. Cogliano, "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels

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

⁸ Dr. Boisseau Responses (Question 16), p. 12.

occurring in exposed humans.”⁹ Finally, Dr. Boobis stated that “[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity.”¹⁰ In other words, carcinogenic effects were only observable at levels at or above the hormonal threshold. In the absence of any scientific evidence of adverse effects at doses below the threshold, arguing about the shape of the dose-response curve below the threshold is not informative. In other words, there is no evidence that estradiol will cause adverse effects below a definable threshold. The EC has failed to present any such evidence in the course of these proceedings.

Q4. *If you were to agree that scientists cannot define the dose-response curve as explained in the previous question, would this state of scientific knowledge be defined as “scientific uncertainty” in this area? If not, please explain.*

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

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

Q5. *Could you please explain what is your position on the existence or non existence of an international standard for MGA for the purposes of Articles 2, 3 and 5 of the SPS Agreement in these disputes?*

17. Please see the U.S. response to Panel Question 20.

⁹ Dr. Cogliano Responses (Question 18), p. 1.

¹⁰ Dr. Boobis Responses (Question 16), p. 19.

¹¹ Appellate Body Report, para. 167.

B. EC Questions to the United States:

Q1. *The 2002 US Report on Carcinogenesis (Exhibit EC 101) states inter alia that: “veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food producing animals to above their normal levels” (p.8). How do you reconcile this with your proposition in para. 51 of your First Written Submission?*

18. The 11th Report on Carcinogens notes that “veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food producing animals to above their normal levels.” Paragraph 51 of the U.S. First Written Submission states that “[w]hile tissue concentrations of estradiol 17 β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels.”

19. The United States fails to see a discrepancy between these statements but is pleased to be able to clarify the issue for the EC through reference to the EC’s own exhibits. It appears that the source of the EC’s confusion is use of the word “normal” in the Report on Carcinogens. In this (biological) context, “normal” is a relative term which depends on the endogenous, baseline levels of estradiol 17 β present in the animal treated with growth-promoting hormones. For example, the “normal” levels of estradiol 17 β in steers (male cattle lacking testes) will be extremely low. It stands to reason, therefore, that treatment of steers with estradiol 17 β to promote growth may increase concentrations of estradiol 17 β in edible tissues to levels that are above “normal” for this type of animal. However, as illustrated in Table III of EC-34¹², this increase may be small (1.1 to 2.3-fold) and, as illustrated in Figure 1 of EC-51A, is not detectable in every animal. Female cattle have higher “normal” levels of estradiol 17 β than steers and these levels may be more variable due to changes in production of estradiol 17 β by the ovary throughout the (21-day) reproductive cycle. Treatment of female cattle (heifers) with estradiol 17 β to promote growth may also result in increased estradiol 17 β concentrations in edible tissues of heifers, and according to Table III of EC-34, this increase is similar to that observed in steers (1.9-fold).

20. The basis for the U.S. statement that “this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels” is clearly illustrated by comparing the levels of estradiol 17 β in edible tissues of treated steers and heifers shown in Table III of EC-34 with the naturally-occurring levels of estradiol 17 β in cattle shown in Table II of EC-34. Concentrations of estradiol 17 β in muscle of treated steers and heifers ranged from 3-17 pg/g, while naturally-

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

occurring concentrations range from 1.3-14 pg/g in steers, 12-13 pg/g in heifers, and 16-860 pg/g in pregnant cattle. Therefore, even though veterinary use of estrogens to promote growth can increase estrogens in cattle to above “normal” levels (11th Report on Carcinogens), this increase is well within the range of naturally observed levels (U.S. First Written Submission).

Q2. *What was the reason to conclude for the first time in the 2002 US Report on Carcinogenesis that estrogens (including oestradiol-17 β) are carcinogenic not only by receptor-mediated effects but that in addition there are possibly by direct and indirect genotoxic mode of action? Was it because of new developments in scientific research that became available after 1999?*

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

22. The 10th and 11th Reports on Carcinogens were published in 2002 and 2005, respectively. Steroidal estrogens were first listed as “known to be a human carcinogen” in the 10th Report.¹⁴ Both the 10th and 11th Reports include a section that discusses the evidence for genotoxic effects of steroidal estrogens. This section is virtually identical between the Reports. Cited in this section are two references: one article published in 1996¹⁵ and the 1999 IARC Monograph on Hormonal Contraception and Post-menopausal Therapy. It is therefore clear that the statements on genotoxicity in both the 10th and 11th Reports on Carcinogens – published in 2002 and 2005, respectively – were based primarily on the findings of the 1999 IARC Monograph and not prompted by new developments in scientific research that became available after 1999.

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

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

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

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

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

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

Q3. *The 2002 US Report on Carcinogenesis states inter alia that: “The RoC does not present quantitative assessments of the risks of cancer associated with these substances. Thus listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives. Such formal risk assessments are the responsibility of the appropriate federal, state, and local health regulatory and research agencies.” If so, have the competent US authorities made the quantitative assessment of the risks of cancer posed by the residues of six hormones in meat from animal treated for growth promotion? If not, when are you going to do it?*

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

26. In line with the 11th U.S. Report on Carcinogens, FDA considers estradiol 17 to be a human carcinogen. (However, it should be emphasized that the carcinogenicity of estradiol 17 in humans is based largely on epidemiological studies of women taking estradiol 17 as post-menopausal therapy, the doses of which are exponentially higher doses than those in residues of estradiol 17 present in beef.¹⁸) FDA concluded that estradiol 17 is not a genotoxic agent, and

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

¹⁷ See, e.g., U.S. First Written Submission, para. 141; U.S. Rebuttal Submission, paras. 38-39.

¹⁸ See U.S. Rebuttal Submission, fn. 72.

that any carcinogenic effects of estradiol 17 in experimental animals are a consequence of persistent overstimulation of the hormonal system. If consumption of residues of estradiol 17 in edible tissues of food-producing animals does not cause such persistent overstimulation of the hormonal system in humans, then FDA concludes that individuals consuming those residues will not be subject to an increased risk of cancer.

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

Q4. *The 2002 US Report on Carcinogenesis states inter alia that: “Estimating the extent to which listing a substance in the RoC protects public health is perhaps the most difficult task in preparing the RoC. The carcinogenic risk (i.e., the probability of developing cancer) depends on many things, including the intensity, route, and duration of exposure to a carcinogen. People may respond differently to similar exposures, depending on their age, sex, nutritional status, overall health, genetics, and many other factors. Only in a few instances can risk for cancer be estimated with complete confidence, and these estimations require studies of long-term human exposures and cancer incidence in restricted environments, which rarely are available.” Despite this recognition of the difficulties, could you please explain if you have nevertheless performed the long-term human exposures to the residues of these hormones in treated-meat in order to quantify if they pose a risk to human health? Do you know if JECFA has performed such a specific quantitative dose-response assessment?*

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

29. For JECFA's approach for assessing the effects of long-term dietary exposure to hormone residues, please see the 52nd Report of the Joint FAO/WHO Expert Committee on Food

Additives (WHO Technical Report Series 893, pp. 57-60, 2000) as well as the information provided by Dr. Tritscher, JECFA Secretariat, at the Meeting with the Experts held in Geneva on September 27-28, 2006.

Q5. *In relation to para. 8 of the US statement of 3 October please explain if you have now made a determination? If not, what does it mean “being in the process of reviewing”? What are you doing exactly? Since the EC’s risk assessment dates of 1999 (and reviewed and confirmed in 2000 and 2002), how long is your review process going to take? Is there any information that the US is now missing? Is there any mechanism by which the US will complete its review within a reasonable period of time now?*

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

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

Q6. *The US stated that the risk assessments performed by JECFA must be presumed to be in compliance with Article 5.1. of the SPS Agreement. But the risk assessments performed by JECFA for these hormones for animal growth promoters do not contain the kind of quantitative or qualitative exposure assessment that Canada and the US criticise the EC for not having done. Nevertheless, the US and Canada appear to assume that JECFA’s assessments are consistent with Article 5.1. SPS. Please explain why under these circumstances would the EC’s risk assessment be inconsistent with Article 5.1. of the SPS Agreement.*

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