UNITED STATES – CONTINUED SUSPENSION OF CONCESSIONS IN THE *EC – HORMONES* DISPUTE

ORAL STATEMENT OF THE UNITED STATES ON EXPERT ISSUES AT THE SECOND SUBSTANTIVE MEETING OF THE PANEL

October 2, 2006

Introduction

1. Mr. Chairman, members of the Panel: Good morning.

2. The United States has repeatedly argued throughout these proceedings that the European Communities' ("EC") permanent ban on estradiol 17β ("estradiol") is not based on a risk assessment within the meaning of Article 5.1 of the *Agreement on the Application of Sanitary and Phytosanitary Measures* ("SPS Agreement"). We have also argued that the EC's provisional bans on progesterone, testosterone, zeranol, trenbolone acetate ("TBA"), and melengestrol acetate ("MGA") do not satisfy the necessary conditions for a provisional measure within the meaning of Article 5.7 of the SPS Agreement. Indeed, the very conclusions underpinning the EC's decision-making are unsupported by the scientific evidence relating to these hormones. The experts' written responses and oral testimony support these U.S. arguments.

Experts' Written and Oral Responses

3. At the outset of this meeting, it is essential to recall the purpose of last week's meetings and today's discussions. The World Trade Organization ("WTO") and this Panel are not being called upon to conduct a risk assessment for the EC. You have not been requested to provide or complete a *de novo* review of the numerous scientific materials relating to the six hormones at issue. This is good news. Not being a scientist myself, I can only imagine how difficult it would

be to attempt to cobble together a justification for the EC's bans. The SPS Agreement does not ask, require, nor permit us to perform such an analysis. Yet the EC apparently hopes that we will decide that a risk assessment must exist somewhere in the mass of unrelated material that it has produced during this dispute, even if we cannot put our fingers on where it exists. I will do my best to make some sense of the EC's approach this morning and to focus the debate on the salient points.

4. The pertinent analysis, as discussed a moment ago, is what the EC has done. Not what the EC could have done, or may still do. Not what this Panel can do for the EC. To conduct an analysis of what the EC has actually done, we may ask much less complex questions such as: has the EC presented scientific evidence of a risk from these hormones when consumed as residues in meat and assessed this risk in the proper fashion?

5. In answering these questions, we can determine whether the EC's purported risk assessment, permanent ban and provisional bans satisfy the requirements of the SPS Agreement. These requirements are relatively simple. For purposes of Article 5.1, an SPS measure – in this case the EC's permanent ban on estradiol in meat from treated cattle – must be based on a risk assessment, as appropriate to the circumstances, of the risk to human health, taking into account risk assessment techniques developed by international organizations. It must identify and evaluate the potential for adverse effects on human health using four steps: hazard identification; hazard characterization; exposure assessment; and risk characterization. Finally, its conclusions must be supported by scientific evidence.

6. For purposes of an evaluation of the EC's provisional bans, the most relevant requirements of SPS Article 5.7 are: that the relevant scientific evidence is insufficient to

conduct a risk assessment for the five hormones and that the bans are indeed based on available pertinent information. In addition, the EC has also failed to satisfy the remaining two prongs of Article 5.7's cumulative test, most notably the requirement that it review its measures within a "reasonable period of time."[1]

7. As I will highlight this morning, the experts' responses confirm that the EC has not based on a risk assessment its ban on meat from cattle treated with estradiol for growth promotion purposes. It has not satisfied the four necessary steps for a risk assessment, and several of the conclusions set out in the EC's Opinions are not supported by scientific evidence. A measure banning meat from cattle treated with estradiol cannot be "sufficiently warranted" or "reasonably supported"[2] by this absence of a risk or assessment of the risk.

8. Likewise, the experts' responses confirm that there is sufficient scientific evidence to complete a risk assessment for each of the five "provisionally banned" hormones and that the EC has not based its provisional bans on available pertinent information. In other words, the EC's measures and "risk assessment" do not satisfy its obligations under the SPS Agreement.

Terms and definitions

"Zero risk"

9. I think that a brief discussion of the term zero risk provides a good starting point for today's discussions. It is an important principle and one to which the EC referred several times in the meeting with the experts. Indeed, the EC at several points asked the experts whether they could ensure that there was "zero risk" of a certain event occurring. The EC used this same

[1] *See* U.S. First Written Submission, Sections IV(C)(1)(c), IV(C)(1)(d).
[2] Appellate Body Report, *EC – Hormones*, para. 193.

tactic in its written comments on the experts' answers. For example, it demanded that Dr. Boobis "provide the necessary assurance" to the EC that residues in meat will never be shown to pose a risk to consumers. (*See*, *e.g.*, EC Comments on Question 20).

10. In the absence of actual risk supported by scientific evidence, the EC attempts to conjure its presence by seeking nothing more than an absolute assurance that estradiol will never, ever cause adverse effects. As we have previously noted, this line of argument is disingenuous. No self-respecting scientist would ever commit to a position that there will never be a new risk related to a substance at some point in the future. The Appellate Body recognized this fact and clarified that "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[3] Several of the Panel's experts agreed with this point and expressed it in terms of the continually "evolving" nature of scientific research (*e.g.*, Dr. Boobis).

11. The SPS Agreement does not call for such an assurance. Rather, for purposes of an evaluation under its terms, the question is: what level of risk is supported by current scientific evidence and principles? Despite this fact and the Appellate Body's guidance, the EC has attempted to create the illusion that there is genuine scientific evidence of a risk to human health by forcing the experts to say that the risk does not equal zero. The experts found themselves in an impossible position.

12. The analysis must refocus on the question of whether the EC has provided any evidence of a risk. The relevant discussion is one of whether the EC, in support of its ban, has adduced

[3] Appellate Body Report, *EC – Hormones*, para. 186, *citing* Panel Report, *EC – Hormones*, at paras. 8.152-8.153.

sufficient evidence to demonstrate a risk from meat from cattle treated with estradiol for growth promotion purposes. Included in this discussion is an analysis of whether the EC has provided scientific evidence that estradiol is genotoxic, mutagenic or carcinogenic (at levels found in residues in meat from treated cattle). Whether a scientist refuses to commit to a stance that there will never be a risk from meat treated with estradiol at some point in the future is not pertinent to this analysis because it is not scientific evidence of a risk. It is simply theoretical uncertainty and cannot be the basis for a risk assessment or an SPS measure.

13. In short, when the experts note that the risk is not "zero", they are not driven to this conclusion by evidence presented by the EC. Yet, the EC attempts to cast these opinions as such. The experts are simply, and correctly, refusing to commit to the untenable position that there will never be evidence of a risk. In reality, theoretical uncertainties always exist.

Risk Assessment Techniques

14. Regarding what, exactly, makes up a risk assessment, the experts and international organizations reiterated the four steps of risk assessment. In addition, the Codex representative stressed that a risk assessment must be based on all available data.

15. As to whether and when a risk assessment must satisfy each of the four steps, there was clear agreement among Drs. Boobis and Boisseau, and JECFA that an evaluation of the human food safety of a drug should include all four steps of risk assessment. JECFA noted that a hazard identification does not qualify as a risk assessment and that the assessment should continue through each of the four steps unless there is "clear cut" evidence, both *in vitro* and *in vivo*, of genotoxicity. Dr. Boobis commented that the only instance in which such an assessment would stop at the hazard identification stage would be if the compound were identified as a DNA-

reactive mutagen. Dr. Boisseau confirmed Dr. Boobis' opinion.

16. Recall that, as we learned last week, genotoxicity and mutagenicity are not synonymous. Genotoxic substances damage DNA but the damage may be repaired. If the damage results in a mutation and the cell divides, then the substance is a "mutagen." As will be discussed in a moment, the experts did not identify any scientific evidence in the EC's Opinions that confirms, *in vivo*, the effects of estradiol at levels below those causing a hormonal response, let alone any evidence that effects at that level are those of a DNA-reactive mutagen.

The EC's Risk Assessment

17. The simple conclusion to be drawn from the experts' comments on the EC's Opinions and the scientific evidence is that the EC has not completed a risk assessment for estradiol. There are at least two reasons supporting this conclusion.

The EC did not complete the four steps of risk assessment

18. As the first avenue of approach, we can find that the EC has failed to complete the necessary steps of a risk assessment. These are the four steps that have been clearly defined by the experts and the original *Hormones* panel. And the EC accepts that these four steps are required. As just mentioned, a risk assessment for estradiol may not stop at the first step of hazard identification unless there is *in vivo*-confirmed evidence that estradiol is either a genotoxin or a DNA-reactive mutagen. The EC has failed to present any evidence that estradiol is genotoxic at levels below those eliciting a hormonal response, nor has it provided evidence that estradiol is mutagenic at relevant levels *in vivo*. The EC was therefore not justified in failing to complete the three remaining steps.

19. The experts confirmed, however, that the EC did not complete the remaining steps. Dr.

Boobis noted, and Dr. Boisseau agreed, that the EC's Opinions are focused on the first step of risk assessment, hazard identification. As noted by JECFA, a hazard identification does not equal a risk assessment. An assessor must finish all four steps. Although he did not speak on this subject in last week's meetings, Dr. Guttenplan has described the EC materials as deserving at best a "mixed rating" in terms of the four steps of risk assessment. (Question 14). He noted particular deficiencies in the hazard characterization and risk characterization sections. (Questions 13 and 14).

20. The EC's failure to conduct a proper risk assessment is sufficient to resolve this dispute. There are certain components that must go into a risk assessment. The EC has not provided them. It has therefore not conducted a risk assessment, as appropriate to the circumstances, for meat and meat products from cattle treated with estradiol for growth promotion purposes.

The EC reaches several conclusions in its "risk assessment" that are not supported by scientific evidence

21. The second avenue for finding that the EC has not completed a risk assessment for estradiol is by determining that the conclusions set out in its assessment are not supported by scientific evidence. The EC's risk assessments reach a number of "major conclusions." On several of these, there is no disagreement among the experts that the EC has failed to present any supporting scientific evidence. If any of these conclusions is not supported by scientific evidence, then the EC's "risk assessment" is not appropriate to the circumstance within the meaning of Article 5.1. There are a number of unsupported conclusions to choose from.

22. For example, the experts agree that the EC has not presented any scientific evidence that estradiol is genotoxic *in vitro* or *in vivo* at physiological levels. The normal action of estradiol

on a cell is mediated through the estrogen receptor. The genotoxic effects, which are abnormal, are not mediated through the estrogen receptor but instead involve direct damage to DNA. To date, concentrations of estradiol required to cause genotoxic effects have been well above those required to elicit normal physiological effects.

23. As noted by Dr. Boobis, positive *in vitro* tests require positive *in vivo* confirmation, as toxicity is not always expressed *in vivo*. For Dr. Boobis, *in vivo* confirmation is critical because, among other things, it takes into account DNA repair mechanisms. He commented that he was "not persuaded" that estradiol is genotoxic at levels below the normal hormonal concentrations present *in vivo*. In other words, that the genotoxicity has a threshold that requires overwhelming the DNA repair mechanisms – an event that will only occur at concentrations well beyond physiological levels.

24. Dr. Boobis noted that the JECFA Reports concluded that any possible risk from estradiol was unrelated to genotoxicity and confirmed that the *IARC Monograph* and *U.S. Report on Carcinogens* did not conclude that genotoxicity was the mode of action underlying carcinogenic effects. If estradiol were in fact carcinogenic via a non-receptor mediated mechanism such as genotoxicity, as the EC claims it is, then estrogen-induced cancers would occur all over the body, not just in estrogen-responsive tissues such as the breast and uterus (Drs. Boobis and Boisseau). Indeed, we would likely see these tumors as a result of the normal human diet, which includes foods with much higher estradiol residue levels than those in meat from treated cattle. Milk, eggs, butter and plants all contribute estrogen to the human diet. Not to mention the normal endogenous production of estradiol by all humans.

25. Dr Guttenplan noted that the evidence that estradiol works through a non-hormone

receptor mechanism was "not strong." Dr. Boisseau's comments appear to endorse his written response on this issue, in which he noted 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."[4] Although Dr. Cogliano noted that the evidence of genotoxicity is weak but "might" still be there, he highlighted the failure of the EC to provide any evidence on this issue.

26. Indeed, the notion that an adverse effect "might" still exist harkens back to the earlier discussion of "zero risk" and the fact that a scientist will not commit to a position that some new risk will never be identified in the future. Until then, it is theoretical uncertainty. The bottom-line is that there is no evidence today of genotoxicity from estradiol at the levels found in meat from treated cattle, and the materials provided by the EC fail to provide any evidence of this risk.

27. The experts could not identify any studies providing evidence of the *in vivo* confirmation of genotoxicity of estradiol at levels below those required to elicit a hormonal response. When put on the spot at last week's meetings with a new study produced by the EC in a last minute attempt to provide evidence of *in vivo* effects, Dr. Boobis quickly dismissed the study as irrelevant. The study's authors had treated the subject rats with so much estradiol that the sheer level of the dose itself killed fifty percent of them, precluding any interpretation of estradiol-specific effects.

28. To put this study's methodology in perspective, residue levels of estradiol in a 250 gram serving of meat from treated cattle are between 15 and 25 nanograms. This is approximately

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

200,000 to 300,000 times less than the dose of estradiol administered to the rats. Further, unlike intermittent meat consumption by humans, the study's authors treated the rats continuously with estradiol for 20 weeks, which is a significant portion of the rats' life span.

29. As noted by Dr. Boobis, there are international guidelines for the conduct of this type of study in experimental animals. These guidelines do not endorse the use of a lethal dose of the test substance, yet the authors of the EC exhibit have done just that. Even when using such an extreme experimental scenario, the authors were not able to provide evidence that estradiol is mutagenic *in vivo*, as pointed out by Dr. Boobis. Clearly, this study is neither relevant to the purported risk to human health associated with eating meat from treated cattle nor does it confirm *in vivo* genotoxicity of estradiol at relevant levels.

30. Another example of an unsupported conclusion in the EC's Opinions is that estradiol residues in meat from treated cattle are carcinogenic. The EC has failed to present any scientific evidence that estradiol will have carcinogenic effects at levels found in residues in meat from treated cattle. Their failure to provide any evidence makes abundant sense. We consume estradiol residues from numerous sources every day at levels much greater than those found in meat residues, whether from cattle treated for growth promotion or not. Milk, butter, eggs and, as noted by Dr. Boobis, a great number of phytoestrogens in plant products are all sources of estrogen in our diets. If estradiol levels in meat posed a risk, then wouldn't the much greater level of hormone found in all these foods be killing us off at a rapid pace? There is no evidence that this is occurring. If we are to avoid hormone residues in meat because we now believe that minuscule amounts of estradiol cause cancer, we should not ignore these other sources and would have to avoid consuming them.

31. As noted by Dr. Guttenplan, there is "no direct evidence" of a risk of cancer from consuming residues in meat from hormone-treated cattle. Dr. Boobis declared that there is no risk of cancer from residues in meat from estradiol-treated cattle and Dr. Boisseau agreed, stating that there is no risk of cancer under the Acceptable Daily Intake ("ADI") level. Dr. Guttenplan contributed to this consensus, commenting that "I don't believe that there is a risk of cancer under the ADI."

32. The lack of epidemiological evidence of a risk informs these conclusions. The Panel inquired about the EC's interpretation of epidemiological studies in writing (Question 26), eliciting the following responses from the experts:

- Dr. Boobis noted that "there 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."
- Dr. Cogliano commented that "the data are not sufficiently specific to establish a link" between cancer and consumption of residues in meat from treated animals.
- Dr. Guttenplan stated that "[t]he epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters."
- Dr. Boisseau noted (Question 25) that "the hormones in dispute have already been used as growth promoters over a sufficient number of years, [and] the epidemiological studies [] 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."

33. Again, our discussion of whether the EC has based its permanent ban on meat from cattle

treated with estradiol for growth promotion purposes on a risk assessment may stop here. The EC has failed to support either of these major conclusions on genotoxicity or carcinogenicity with scientific evidence. The SPS Agreement does not permit the EC to do so. An assessment that fails to adduce scientific evidence in support of its underlying conclusions is not a risk assessment, as appropriate to the circumstances, within the meaning of SPS Article 5.1.

The EC's provisional ban

34. There is a similarly uncomplicated analysis by which it can be determined that the EC's "provisional bans" do not satisfy the requirements of SPS Article 5.7. We need only look at either of the first two of the four cumulative requirements of that provision. The EC's bans do not satisfy these requirements, as was confirmed by the expert testimony.

The scientific evidence is sufficient to conduct a risk assessment for the five hormones

35. The first of Article 5.7's requirements for a provisional ban is that the evidence be insufficient to conduct a risk assessment. None of the experts believes that this is the case for testosterone, progesterone, zeranol, TBA or MGA. Dr. Boobis opined that the data is sufficient. Dr. Boisseau agreed. Dr. Guttenplan noted that the evidence is sufficient to complete the four steps of risk assessment. When pressed by the EC on his written response on TBA and zeranol, Dr. Guttenplan noted, on further reflection on the evidence, that it is possible to assess any potential risk from both hormones.

36. The EC has argued that available information is insufficient to conduct a risk assessment is insufficient because JECFA's maximum residue levels ("MRLs") for the hormones were based on "old data" obtained in the 1970's and 1980's, and that these data can no longer be accurate simply because new methodologies have been developed since. The experts, both in

their written and verbal answers, have contradicted this claim by the EC. Dr. Boobis called the assays relied on by JECFA "fit for purpose" and explained that even though the same assay methodology (radioimmunoassay, or "RIA") may be used to measure hormones in meat and levels of hormones in human blood, the goals of these measurements are very different. Therefore, it cannot be said that because an assay is not sensitive enough for one purpose it is therefore not sensitive enough for another purpose.

37. Dr. Boisseau agreed with Dr. Boobis on this issue, both in his written and verbal comments. He stressed that methods used to quantify hormone residues in meat are "compatible with the MRLs," and that the data were sufficient for risk assessment. JECFA stated that there is no reason to question the validity of the residue data. JECFA also explained that for its evaluations of the hormones in 1988 and 1999, the entire data set was scrutinized in detail, special attention was paid to the quality of the data, and the methods used were very specific for each hormone evaluated.

38. Dr. De Brabander, who said initially in his written comments that the MRLs for zeranol, TBA and MGA were not acceptable from an analytical point of view, appeared to agree with Drs. Boobis and Boisseau last week when he said that the "old methods" may still be valid, but that they should be checked with newer methods which may yield additional information. In addition, Dr. De Brabander commented that since 1999 there have been no new residue data that call for the re-evaluation of the hormones by JECFA. This statement indicates that the residue data reviewed by JECFA is still "sufficient" for purposes of an analysis today. Collectively, then, the experts' comments demonstrate that even though the MRLs for the hormones are based on data that were generated many years ago, the EC's claim that these data are insufficient is

simply not supported by basic scientific principles.

39. Since the experts have confirmed that the evidence for each of the five hormones is sufficient to complete a risk assessment, discussion of the "provisional" bans may stop here in light of the cumulative nature of Article 5.7's requirements. The EC's ban is not a provisional measure for purposes of the SPS Agreement.

The "provisional bans" are not based on available pertinent information

40. The second of Article 5.7's requirements is that a provisional measure be maintained on the basis of available pertinent information. The EC's "provisional" bans do not satisfy this requirement because there is no available pertinent information indicating that any of the five hormones poses a risk to consumers when used as a growth promoter in cattle.

41. As noted by Dr. Guttenplan, if there is any theoretical risk from estradiol, risk from the five provisionally banned hormones would be "even lower." Dr. Boobis comments that there is no evidence of adverse effects of the five hormones in humans at levels found in residues in meat from treated cattle. Dr. Boobis also reminded us of the several failed attempts by the EC to demonstrate violative residues in meat through highly unrealistic testing scenarios. His expanded views on these studies are provided in his written responses (Question 62). I will discuss the results of these studies in a few moments.

42. The only dissenting view was provided by Dr. Sippell. Dr. Sippell's comments appear to be little more than a policy statement designed to remind us to take children into account since he provided no evidence of a risk to this population from residues of the five hormones in beef in either his written or verbal answers.

43. In sum, the views of the experts are evidence of a lack of available pertinent information

indicating that the five hormones pose a risk when consumed as residues in meat. Indeed, all available pertinent information indicates that consumption of these residues is safe. The EC has therefore not based its "provisional" bans on available pertinent information within the meaning of SPS Article 5.7.

44. Based on the experts' responses, it is clear that the EC has neither based its permanent ban on estradiol on a risk assessment nor developed legitimate provisional bans. An analysis of these points would not entail the type of *de novo* review to which I alluded earlier. As noted, none of us are equipped for such a review and the SPS Agreement does not require or condone such a review.

Other Issues – Prepubertal Children

45. While the Panel's analysis need not extend to this issue, I will now take a moment to discuss the EC's arguments relating to prepubertal children. The EC claims that estradiol residues in meat from treated cattle pose a risk to this sub-population. However, the EC fails to provide scientific evidence of this risk.

46. In particular, the EC relies on an assay that, to date, remains unvalidated; the EC has failed to produce any scientific evidence demonstrating that JECFA's ADI's do not sufficiently protect children; and the EC has failed to complete the necessary steps of a risk assessment for this population.

The Klein Assay

47. All of the EC's conclusions and calculations regarding the risk to prepubertal children from estradiol residues in beef are drawn from the results of the unvalidated "Klein assay." In order to better understand why this assay has not been validated, it is useful to recall the experts'

comments on what it means to "validate" an assay. Dr. Boisseau noted that there are several steps involved in validating an assay, that international guidelines exist for such validation, and that inter-laboratory validation is more important than intra-laboratory validation. Dr. Guttenplan agreed that independent confirmation of results in a number of laboratories is essential to validation. The EC has not provided evidence that this has been done for the Klein assay.

48. In his written and verbal responses, Dr. Boobis provided several reasons why the Klein assay has not been validated. He cited the inconsistency of results obtained using the Klein assay. For example, levels of estradiol in prepubertal boys reported in a 2006 study by Klein were five-fold higher than the results originally reported by Klein in 1994. Dr. Boobis also questioned the specificity of the Klein assay. Dr. De Brabander noted that, for purposes of assay validation, specificity is the "most important" step. Dr. Boobis explained that the Klein assay is not specific for estradiol since it is based simply on binding the estrogen receptor, which binds all estrogens indiscriminately and possibly other endogenous steroids, not just estradiol.

49. Dr. Boobis also noted that DES, a synthetic estrogen well-established as much more potent than estradiol, nonetheless is detected as less-potent than estradiol using the Klein methodology. Dr. Boisseau's comments, although less specific than those of Dr. Boobis, appeared to support Dr. Boobis' thought on the unvalidated nature of Klein.

50. Only Dr. Sippell alleged that the Klein assay is a valid method for measuring estradiol in prepubertal children. However, in his attempt to demonstrate that Klein has satisfied the important step of inter-laboratory validation, Dr. Sippell cited the results of another assay that achieved substantially different results and which was conducted in entirely different media. In

other words, Dr. Sippell provided no evidence supporting the validation of the Klein assay.

51. What can be concluded from the discussion with the experts and from the statements of Dr. Sippell is that there is uncertainty among the experts regarding the levels of circulating estradiol in prepubertal children. However, this uncertainty was by no means resolved in last week's meetings and there was no consensus reached regarding the accuracy of the Klein assay. It is not the purpose of these proceedings for us, a group of non-scientists, to make a *de novo* determination of what the levels of estradiol in children are or might be. For purposes of the analysis at hand, the salient points are that no one knows to what extent the Klein assay measures estradiol as opposed to other endogenous steroids and that an unvalidated assay cannot serve as the baseline for analysis in a risk assessment. Yet, the EC has used such an assay as a cornerstone for many of the conclusions in its "risk assessment."

JECFA ADIs

52. In addition, none of the materials set out in the EC's Opinions cast into doubt the safety of the JECFA ADI for estradiol. Dr. Boobis noted that he has run calculations on this point and that, even assuming lower circulating levels of estradiol in prepubertal children, the JECFA ADI is still sufficient. He confirmed that JECFA's reevaluation of the safety of estradiol in 1999 included the review of studies in developing animals and that in light of this specific evidence it was possible for JECFA to evaluate the potential risk to sensitive populations. In completing its assessment, JECFA took into account a conservative international food basket and used safety factors specific to this sensitive population.

53. Dr. Sippell spoke at length about several natural events and diseases in children, and proposed that the "new finding" that estradiol levels in prepubertal children may be lower than

previously thought provides an explanation for these events and diseases. As we have shown in our comments, none of the materials relied on by Dr. Sippell in his responses to the Panel's questions provide evidence of a risk to children from consuming estradiol residues in meat from treated cattle.

54. In sum, the EC has presented no scientific evidence that demonstrates that JECFA ADIs are insufficient to protect the health of prepubertal children. It has presented no evidence that estradiol residues in meat from treated cattle pose a risk to any consumer, including children. This fact is not surprising given the much greater levels of estradiol children are exposed to from several other sources in their daily diets. This fact is also not surprising given the conservative food basket and safety factors taken into account by JECFA when it performs its safety assessments. The JECFA representative and Drs. Boobis and Boisseau each highlighted these important facts.

55. Compared to the levels present in meat from cattle treated with estradiol for growth promotion purposes, consumers in the EC and around the world are subjected to much higher levels of estradiol at nearly every turn in their daily lives. Despite this reality, the EC has chosen to ban meat from cattle treated with estradiol for growth promotion purposes – a relatively minuscule source of the overall human consumption of estradiol, for which there is no scientific evidence of a risk.

The EC did not assess the risk to children

56. Finally, the EC's Opinions not only suffer from evidentiary but procedural flaws. As Dr. Boobis noted, the EC simply failed to complete an exposure assessment for children. Dr. Boobis also pointed out that the EC's Opinions did not evaluate the actual risks to children. In other

words, the EC has failed to complete the mandatory third and fourth steps of risk assessment – exposure assessment and risk characterization. It therefore has not completed a risk assessment, as appropriate to the circumstances, within the meaning of SPS Article 5.1.

57. In conclusion on this topic, by invoking this sub-population, which by its very nature raises the utmost concern, sympathy and antennae of everyone in this room, the EC apparently hopes to carry the day in these proceedings. It must hope to do so because of the numerous shortcomings in other areas of its Opinions. Its unsubstantiated concerns relating to children do not, however, satisfy its obligations under the SPS Agreement.

58. This does not mean that the doubts and theoretical uncertainty on circulating estradiol levels in prepubertal children identified in last week's meetings are unimportant. They are important. Indeed, JECFA reaffirmed that ensuring the safety of children is a "basic principle" of risk assessment and a fundamental focus of its work. As such, it is a safe guess that JECFA would be interested in any new evidence relating to this sub-population. As we have learned from the JECFA and Codex representatives, however, the EC has not shared any information with them. If the EC believes that the information it possesses has been properly validated and that the evidence is sound, then every Codex member around the world would benefit from its conclusions. The EC is not alone in its desire to protect the health of prepubertal children and other sensitive sub-populations.

59. It would be irresponsible to insinuate that the United States and international organizations such as JECFA have not taken every possible step to protect the health of prepubertal children. Indeed, the JECFA representative noted that this population is first and foremost in its evaluations. The EC cannot, however, base a measure simply on unsupported,

theoretical concerns. The EC has not provided evidence of the relevant risk nor carried out the necessary steps for an assessment of such risk. In order to find that the EC has actually assessed the potential risk to prepubertal children from consumption of estradiol residues in meat, one would have to make several unjustified evidentiary leaps (such as determining, despite considerable evidence to the contrary, that the Klein assay is validated) and excuse the absence of two fundamental steps in the risk assessment process (exposure assessment and risk characterization).

Misuse

60. Finally, we come to the issue of misuse of growth promoting hormones in the United States. I have left this subject for last and have not discussed it in the context of the other scientific issues because, quite frankly, it is unclear what role misuse plays in the EC's Opinions and arguments. The EC apparently considers potential misuse to be a risk, but has failed to provide any evidence or argument as to how it has actually assessed this risk. As was emphasized in last week's meetings, the EC sets out unrealistic, contrived misuse scenarios in its Opinions that have no grounding in evidence. For example, the EC has developed a scenario in which the ears of cattle enter the human food supply.[5] Both Drs. De Brabander and Boobis opined that they were unable to locate any evidence in the EC's Opinions that this scenario would or could ever come to fruition. Dr. De Brabander did, however, note that one of the EC's exhibits provided evidence that meat with hormone residues were shipped under the hormone-free cattle program. I'd like to make a few brief comments on this point.

61. First, in the real world, there is always a chance that producers will misuse veterinary

[5] *See* EC 1999 Opinion, Section 3.3.

drugs. So-called "extra-label use" is not unique to growth promoting hormones. Neither is it unique to countries that permit the sale of veterinary drugs "over the counter." Extra-label use is possible in all countries and in all regulatory systems, whether administration is restricted to veterinarians, feed lot owners, or whether there is an outright ban on the use of a substance. The critical question is whether there is an effective system in place to detect misuse and take corrective action.

62. Identifying and correcting infrequent misuse is not evidence that a system is not functional, that it is insufficient, or that it is unsafe. It is not evidence that good veterinary practices are not adhered to. Quite frankly, if good veterinary practices are now construed, as they appear to have been by the EC, as a one-hundred-percent assurance that no failure will ever take place in a food safety system, no WTO Member, including the EC, is shipping products according to good veterinary practices. We can assume that the EC considers satisfaction of good veterinary practices to be an absolute guarantee in light of the fact that it has imposed an absolute ban to guard against any theoretical failures of control.

63. Think about the practical application of the EC's theory. If a one-hundred-percent certainty of the application of good veterinary practices were required to establish the safety of animal-derived foods, international trade in these foods would grind to a halt. As we have learned from JECFA and the experts, the international standards that control the flow of these products are premised on assessments that factor in exposure levels under good veterinary practices. Under the EC's interpretation, the concept of "good veterinary practices" becomes meaningless because no country can provide absolute certainty that there will not be failures in its system.

64. Rather, the types of corrective actions taken in the United States that the EC construes as evidence of a weakness are instead evidence of a robust food safety system. No food safety system is perfect. Even a ban on a substance will never absolutely insure that the product will never enter the human food supply. For example, according to Ranier Stephany,[6] despite the attempts of EC regulators to ban the very same hormones at issue in these proceedings, the EC has an active black market in these products.

65. The EC provides no evaluation of the actual system of controls in place in the United States. We have described these controls at length in our previous submissions to the Panel. Dr. De Brabander claimed to have examined the U.S. system of controls when he opined that the U.S. system is nothing but "audits and paper work." However, he provided no analysis of the actual U.S. system. Neither did the EC. In fact, when asked in last week's meetings whether he was familiar with the U.S. and Canadian meat safety systems, Dr. De Brabander noted that he was not a meat inspector and was not qualified to make judgments on these systems. His overly simplistic view of the U.S. system belies his lack of experience in this subject matter area and admitted lack of knowledge of the actual controls in place in the United States.

66. Second, even if one were to assume the unrealistic and hypothetical misuse scenarios developed by the EC, the EC has failed to present convincing evidence that misuse leads to violative residue levels. Indeed, in the majority of the studies put forward by the EC on this point, it has been unable to demonstrate violative residue levels despite extreme artificial misuse scenarios. The United States has addressed these issues in its earlier submissions. In the few isolated studies where the EC did identify high residue levels that exceeded Codex MRLs, these

[6] *See* Exhibits US-29, US-30; *see also* Exhibits US-31, US-32.

were only achieved through the use of very extreme and unrealistic scenarios. Dr. Boobis elaborated on these studies and their failure to provide any convincing evidence of misuse in his written answers to the Panel's questions (Question 62).

67. Third, and finally, the EC fails to assess the risk of misuse. While the experts did not have a chance to turn to this point last week, the necessary evidence of the EC's failure may be found in their written responses. For example, Dr. Boisseau noted that "it is not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses." (Question 48). Dr. Boobis agreed, writing that "[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." (Question 48). (*See* the responses of Drs. Boobis and Boisseau to Question 48).

Conclusion

68. When you take a step back from the EC's Opinions, it becomes more and more clear that they are flawed in larger ways than the EC would like us to see or focus on. In light of its line of questioning to the experts last week, the EC apparently hopes to make this dispute one about getting lost in the weeds of several scientific dead-ends. The specters of misuse, risks to sensitive populations and the unwillingness of the experts to commit to a position that there will never be evidence of a risk from any of these hormones in the future are examples of these scientifically unfounded pitfalls. We could go on *ad nauseam* in a debate as to whether science in these areas is evolving. As we know from our discussions with the experts last week, science is continually evolving. This evolution cannot be equated with evidence of a risk, however. We are not scientists, and an attempt to thrust ourselves into the debates on these issues would be

nothing more than a misguided *de novo* review of the science by us, laypersons.

69. If we follow the paths laid out by the EC, we will lose sight of the larger problems of the EC's Opinions and the fundamental obligations and requirements against which they are to be measured – those set out in the SPS Agreement. When we view the EC's measures in this context – in which we have the necessary knowledge and can perform the necessary analysis – it is clear that there are several avenues by which we can conclude that the EC has not based its permanent ban on estradiol on a risk assessment within the meaning of SPS Article 5.1, nor has it implemented a provisional ban on the other five hormones within the meaning of SPS Article 5.7. I have discussed these avenues and the appropriate conclusions that can be reached for each based on the scientific record in this dispute this morning.

70. The United States looks forward to further discussing tomorrow how the experts' comments factor into the parties' legal arguments.