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UNITED STATES – CONTINUED SUSPENSION OF OBLIGATIONS IN THE EC – HORMONES DISPUTE

Report of the Panel

Addendum

This addendum contains Annex F to the Report of the Panel to be found in document WT/DS320/R. The other annexes can be found in the following addenda:

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ANNEX F

COMMENTS BY THE PARTIES ON THE REPLIES OF THE SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC TO QUESTIONS POSED BY THE PANEL AND COMMENTS BY THE PARTIES ON THE OTHER PARTIES' COMMENTS

ANNEX F-1

COMMENTS BY THE EUROPEAN COMMUNITIES ON THE REPLIES OF THE SCIENTIFIC EXPERTS TO QUESTIONS POSED BY THE PANEL

(30 June 2006)

A. GENERAL DEFINITIONS

Q1. Please provide brief and basic definitions for the six hormones at issue (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate), indicating the source of the definition where applicable.

EC Comments

Dr. Boisseau's reply does not consider any progress in toxicological knowledge concerning these hormones, and in particular estradiol, since the 70th and 80th JECFA reports. Since then new data concerning residues in tissue and their toxicological impact have been published. In his answer, he has only adopted a narrow regulatory definition. More specifically, as regards oestradiol, aromatization of androgens in estrogens is also very significant in adipose tissue. In his definitions, the sites of production in the human body is limited to the primary source and does not dwell on variability over the life span of an individual. Furthermore, his definition does not stress that Zeranol is a very potent estrogen. Zeranol is not a "natural estrogen" that humans are exposed to. In fact, great care should be taken to avoid the presence of fusarium molds in animal feed and especially in products for human consumption. As regards the implantation of these hormones, he uses simple present tense ("the ear is discarded") when precisely this is not known nor it is sure that it happens in practice in all cases. He should therefore have said that "the ear should be discarded at slaughter". Moreover, implantation can be made at the dewlap level, not only at the ear one, especially in case of multiple implantations. Furthermore, in some new recommendations of trenbolone use, it is possible to proceed to repeated implantation of steers or heifers.

Q2. Please provide definitions for the following terms as they relate to the hormones at issue, indicating the source of the definition where applicable: anabolic agents, steroids, steroidal oestrogens, parent compounds/metabolites, catechol metabolites, mitogenicity, mutagenicity, androgenic/oestrogenic activity, genotoxicity, genotoxic potential, carcinogenicity, and tumorigenicity. In your replies, please be sure to identify and describe any relevant differences between the terms.

EC Comments

Dr. Boisseau's reply that "In my e-mail of 26/04/06, I have indicated that I did not think that I am in the position to reply to this question" calls into question the reliability of his answer to question no 1 and indeed to the other questions. As the EC has pointed out during the selection procedure, Dr. Boisseau does not posses any expertise on these substances, as he does not appear to have carried out any specific research on these substances during his professional life. Dr. Boisseau has explicitly admitted it in his e-mail to the Panel secretariat where he wrote: "*I did not join any publications as I have none on hormones*".

B. RISK ASSESSMENT TECHNIQUES

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

EC Comments

The European Communities agrees with the statement by Dr. Boisseau that currently there is no international guidance document relevant to the conduct of a risk assessment with respect to veterinary drug residues and in particular the six hormones under consideration. Indeed, the documents to which Dr. Boobis refers to in his reply are not "assessment techniques developed by the relevant international organizations", in the sense of Article 5.1 of the *SPS Agreement*. They are informal ad hoc papers without any legal value. Moreover, when the European Communities evaluated these hormones, it applied its standard legislation for the evaluation of this type of substances, which complies fully with the general definitions of risk analysis as described in the Codex Alimentarius' latest Manual of Procedures.

Moreover, Dr. Boisseau's statement that "*the situation is similar in the European Union*" and that "*The CVMP has assessed all the pharmacologically active substances used in veterinary medecine without any written guideline about risk assessment*" is wrong. It is not the CVMP (Committee on veterinary medicinal products) which is responsible for these hormones when administered for animal growth promotion, but it has been the SCVPH (scientific committee on veterinary measures relating to public health). This latter Committee, and the European Communities in general, have been applying advanced principles and techniques of risk analysis which Codex Alimentarius is only now considering of formally putting in practice. See for instance the European Commission Decision 97/579/EC of 23 July 1997 which set up scientific committees in the field of consumer health and food safety which has established the SCVPH (OJ L 237, 28.8.1997, p. 18-23) and the Opinion of the Scientific Steering Committee on harmonisation of risk assessment procedures adopted on 26-27 October 2000, which can be found at http://ec.europa.eu/food/fs/sc/ssc/out82_en.html. These advanced principles of risk analysis have been routinely applied by the European Communities for quite some time well before 1997.[1] They were applied when the SCVPH evaluated these six hormones in 1999, 2000 and 2002, and have since then formally been restated in the relevant EC legislation, in particular Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 31, 1.2.02, p. 1-24, in particular Article 6.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)].

EC Comments

As already explained above in its comments to the replies to question No 3, the European Communities agrees with Dr. Boisseau's reply that "there is no Codex standard specifically on the risk assessment of effect of residues of veterinary drugs". Neither the work of IPCS nor the

[1] See, e.g., Commission Directive 93/67/EEC of 20 July 1993 laying down the principles for assessment of risks to man and the environment of substances notified in accordance with Council Directive 67/548/EEC, OJ L 227, 8.9.1993, p. 9-18.

Environmental health Criteria no 70 nor the monograph published in the WHO series no 43, mentioned by Dr. Boobis and Dr. Guttenplan, respectively, constitute legally binding "assessment techniques" for risk assessment in the sense of Article 5.1 of the *SPS Agreement*. The EC has been much more advanced than JECFA in the application of generally acceptable techniques for risk analysis, as explained in the references to the relevant EC legislation in the previous question No 3. The EC documents mentioned above, although publicly accessible, can be made available to the Panel and its experts upon request.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) and explain how they differ.

EC Comments

The European Communities submits that the Panel's question is of little relevance to the issues under consideration in the present proceedings. Indeed, the Panel's question appears to ignore the fact that the Appellate Body in the *Hormones* case has clarified that the term "risk assessment" in the *SPS Agreement* is wider in scope because it covers also evidence, considerations, objectives and factors that are also taken into account at the "risk management" phase.[2] Consequently, the answers of all scientists do not take into account the legal requirements of the *SPS Agreement* in this area, as interpreted by the Appellate Body. However, the European Comunities has in any case followed the three components of risk analysis, as explained above and in its reply of 3 October 2005 to question No 24 of the Panel.

Moreover, none of the replies by the scientists describes what is actually going on in Codex. The reality is that JECFA performs, most of the time, as it did with regard to these hormones, both risk assessment and risk management functions (something which Dr. Boisseau admits), thus the subsequent decisions/recommendations by the Codex Alimentarius Commission become a mere formality. Indeed, JECFA's reports and monographs are drafted in such a way as to leave practically no room to the members of the Codex Alimentarius Commission to decide on the appropriate level of health protection and the risk management options that are available to its members. That is another reason for which the European Communities decided that the Codex recommendations on these hormones could not achieve the level of health protection considered appropriate in its territory.

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

EC Comments

The European Communities does not understand the relevance of this question for the purposes of these disputes and the corresponding replies of Dr. Boisseau and Dr. Boobis. This type of formal distinction between the various components of risk assessment are not mentioned in the *SPS Agreement* and they are clearly not legally binding, since they are not risk "assessment techniques" in the sense of Article 5.1 of the *SPS Agreement*. Moreover, as the Appellate Body has held in the *Hormones* case (at para. 181), to the extent these distinctions are used "to achieve or support what appears to be a restrictive notion of risk assessment" this has no textual basis in the SPS Agreement. More importantly, however, if these four steps are not formally identified in the risk assessment document of a member, this does not mean that the risk assessment of that member is faulty or scientifically unsound. For instance, the statements by the above 2 scientists appear to discard the relevance of some residues that are not pharmacologically active but may interfere with normal metabolic functioning of cells given their intrinsic chemical potential to form covalent adducts to

[2] *See* Appellate Body Report in EC - *Hormones*, at paras. 181 and 206.

biomolecules (trenbolone for example which gives a high level of protein adducts). Normally, this biological impact should be considered separately and in addition to the hormonal effects. But until now, this has never been done by JECFA and the defending parties when they evaluated these hormones for animal growth promotion purposes. Hence, it is difficult in this context to know what is really a marker residue of a compound having some toxic impact that are not at all related to hormonal effects.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations, in your view, addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? Have they been addressed in the 1988 and 1999 JECFA risk assessments of these hormones? [see Canada's comments in para. 72 of its Rebuttal Submission]

EC Comments

The European Communities notes first that Dr. Boisseau admits that "in 1987 and 1999, at the time of the assessment of oestradiol-17β, there was no risk assessment guidance available on this issue". Even so, he goes on to argue that neither in 1987 nor in 1999 JECFA considered this kind of non-linear situation, despite the fact that it had found in its 1999 report that "oestradiol-17β has a genotoxic potential." However, this approach of JECFA is scientifically unsound, as Dr. Boobis now accepts when he says that today "in practice, it is likely that as veterinary drug residues in food are avoidable by not using the drug, the Committee would have declined to establish an ADI".

The European Communities notes, however, that there are basic flaws in the replies of both Dr. Boisseau and Dr. Boobis. Indeed, the accumulation of so much new peer-reviewed evidence since 1999 establishes clearly that oestradiol-17β is a direct carcinogen and does not act only through hormonal receptors. In addition to the peer-reviewed studies mentioned in the 1999, 2000 and 2002 EC risk assessments, it would be appropriate to refer also to the work of Hari K. Bhat, Gloria Calaf, Tom K. Hei, Theresa Loya, and Jaydutt V. Vadgama: *Critical role of oxidative stress in estrogen-induced carcinogenesis*, published in the Proceedings of the National Academy of Sciences, Vol. 100 (2003) 3913-3918, demonstrating the necessary role of catechols of estradiol or other catechols (2/4-hydroxy-estradiol-alpha produced from estradiol-alpha, menadione) in induction of oxidative stress to induce tumors in the hamster kidney carcinogenesis model. See also the two papers by J. Russo and his co-workers: *17β-Estradiol is carcinogenic in human breast epithelial cells*, and *Estrogen and its metabolites are carcinogenic agents in human breast epithelial cells*, published in the Journal of Steroid Biochemistry & Molecular Biology, vol. 80 (2002) 149-162 and vol. 87 (2003) 1-25, respectively.

From a more systematic point of view, the views of Dr. Boobis can also be criticized because a threshold is a theoretical concept that provides the justification for the use of the NOAEL and thus the ADI. In the work of JECFA, the NOAEL is perceived as evidence of the practical revelation of a threshold. But a true threshold can only be established with an infinitely large group of animals: thus, the dose distance between the true threshold and the NOAEL cannot be established. In a genetically and phenotypically heterogenous human population, there is a risk from endogenous hormone – induced adverse outcomes. Additionally, there must be a distribution of both consumption of meat and hormone response sensitivity in the human population. We know that endogenous hormones in animals and humans are known to cause a wide variety of adverse effects from reproductive function to malignancies. These considerations demonstrate that some fraction of the population will be at higher risk for hormone-related adverse outcomes, no matter the dose, due to consumption of

hormone-implanted meat. A number of publications, some of which have been submitted by the European Communities to this Panel, have explored the threshold concept and the activity of hormones at very low doses. These are:

Gaylor, D. W., Sheehan, D. M., Young, J. F. and Mattison, D. R.: The threshold dose question in teratogenesis (Letter). Teratology, 38:389-391, 1988.

Sheehan, D. M., and vom Saal, F. S.: Low dose effects of endocrine disruptors- a challenge for risk assessment. Risk Policy Report, 31-39, issue of Sept.19, 1997.

Sheehan, D. M., Willingham, E., Gaylor, D., Bergeron, J. M., and Crews, D.: No threshold dose for oestradiol-induced sex reversal of turtle embryos: How little is too much? Environmental Health Perspectives 107:155-159, 1999.

Sheehan, D. M.: Activity of environmentally low doses of endocrine disruptors and the Bisphenol A controversy: Initial results confirmed, in Proc. Soc. Exp. Biol. Med. 224:57-60, 2000.

Blair, RM, Fang, H, Gaylor, D, Sheehan, D. M.: Threshold analysis of selected dose-response data for endrocrine disruptors, in APMIS 109:198-208, 2001.

Q8. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please identify and describe any steps that are taken in the risk assessment process to build a margin of safety into the final recommendation.

EC Comments

The replies of Dr. Boisseau and Dr. Boobis are theoretical statements with little scientific relevance as regards the safety of these hormones. For instance, the appropriate studies in humans would require a huge study population, and would be seriously confounded by medical treatments with hormones and environmental exposures to hormones. Also the conclusion that there is a threshold for hormone action in the absence of other sources of hormone cannot provide a sound scientific basis in order to conclude that endogenous hormones are below the threshold for all actions of the hormones. Therefore, added hormone from implanted beef should increase risk for endpoints that are already occurring from endogenous hormones. Appreciable risk is a subjective decision, as are the 10-fold safety margins. Because of the small numbers of animals on studies, the resolution is generally low.

More specifically, the evidence used by JECFA in the evaluation of these hormones is too old (dating from the 1970s) and has been obtained with outdated detection methods to be relevant today. Dr. Boisseau also writes that "*...taking into consideration the diversity of humans, resulting from the sex, age, race, which can lead to different sensitivity...*", but JECFA did not take the low endogenous levels and thus the high sensitivity of children into account. Also Dr. Boobis states that "*where there was an identifiable sub-group who might reasonably be expected to be more sensitive than the group in whom data were obtained, for example children relative to adults, an extra factor was applied*." Indeed, the JECFA expert committee that examined these hormones did not include any physicians and child endocrinologists! It can be argued that for most chemical compounds, such as pesticides, the knowledge on their potential toxicity resides with toxicologists. However, when we are dealing with the natural hormones and compounds that directly affect the endocrine system, the knowledge on how they potentially can affect humans is a part of the daily work of paediatricians and other physicians. Thus, it is essential that persons with a medical background are present in the JECFA committee (see more on this below). Dr. Boisseau also writes something about low oral activity of 17β-oestradiol, but that is simply not scientifically correct as demonstrated below (comment in relation to question 43). For instance, oral contraceptives and some hormone replacement therapy are taken by the oral

route and are shown to be very active. This demonstrates that oestradiol and progesterone are bioavailable through the oral route.

Q9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

EC Comments

The Canadian statement cannot be scientifically correct in the unqualified manner in which it is expressed and certainly is not correct as regards the six hormones under consideration. It would all depend on when JECFA's scientific data base is considered to be complete and that there are no outstanding scientific issue. For example, when JECFA evaluated in 1988 these hormones, it considered unnecessary to establish an ADI, presumably because it considered that there was no outstanding scientific issue. However, in its 1999 evaluation of the three natural hormones JECFA changed its evaluation and this time established an ADI. Both in 1988 and in 1999 JECFA's evaluation was based on the assumption that these substances act only through the hormonal receptors. However, this assumption is certainly incomplete and scientifically incorrect because it is today generally accepted that some of these hormones are genotoxic and can cause cancer directly. Furthermore, as already explained above, the ADI and MRLs that JECFA established in 1988 and in 1999 for the three synthetic hormones do not take into account the low endogenous levels and thus high sensitivity of prepubertal children. In conclusion, there are so many examples of cases where JECFA has set an ADI because it considered its scientific data base to be complete and that there were no outstanding scientific issues, but it had subsequently to change its mind in the light of more accurate reading of the evidence or more recent scientific data. A good recent example is the case of Carbadox, cited by the European Communities in paras. 150 and 151 of its 2nd Written Submission in the US Panel. It follows that the issue of when the scientific data base is complete can be very subjective and prone to many errors of which JECFA's assessments are certainly not immune.

Q10. In para. 129 and 168 of its Replies to the Panel Questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not". Does Codex have risk management options other than (1) the establishment of an MRL, (2) establishing that an MRL is not necessary or (3) no recommendation?

EC Comments

The European Communities considers that the reply of Dr. Boisseau confirms that JECFA has a narrow mandate, even if it frequently oversteps its role and proposes also risk management measures, thus leaving practically no option to Codex Alimentarius Commission and its members than to follow its narrow recommendations to adopt or not an MRL. What is also important to note is that JECFA has not considered as part of its narrow mandate to examine whether there is any likelihood of misuse or abuse of these hormones and whether the identified risks to human and animal health from the use of these hormones for growth promotion by far exceed any potential benefits.

Q11. What should, in your view, be the components of a qualitative risk assessment, compared with a quantitative risk assessment? [see para. 82 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with the statement by Dr. Cogliano. The statements by Dr. Boisseau and Dr. Boobis are simply contrary to the findings of the Appellate Body in the 1998

Hormones case, where it held that a qualitative risk assessment is equally acceptable under the SPS Agreement and that it does not require the same type of analysis as a quantitative risk assessment. More generally, the issue of whether a threshold model or a non-threshold model is used is critical in determining risk. The literature on no-threshold cited above, in addition to the no-threshold models used for example for PCBs and dioxin, are more appropriate than the current procedures applied by JECFA. For instance, endogenous estrogens are active at inducing some responses in most, if not all, age and population groups. Additivity of exposure to endogenous and exogenous hormones will necessarily result in increased risk at any exogenous dose, no matter how low. Interestingly, the US EPA uses no-threshold models for non-genotoxic chemicals, such as dioxins and PCBs, due to a combination of very long half-lives and activity at very low doses. The European Communities submits that consumption of hormone-treated beef at regular intervals will provide continual or intermittent exposure of estradiol and other growth hormones and thus increase risk and undermine its high level of health protection from these substances.

Q12. How is scientific uncertainty addressed in risk assessments in general? With respect to the assessment of risks from the consumption of meat treated with the growth promotion hormones at issue, how has scientific uncertainty been considered by JECFA/Codex ? How does it differ from the way it has been considered by the European Communities in its assessment of risks from the consumption of meat treated with the growth promotion hormones at issue?

EC Comments

The European Communities disagrees with the statements by Dr. Boisseau and Dr. Boobis because of their extremely narrow understanding of the concept of scientific uncertainty. They both consider that scientific uncertainty is adequately addressed by JECFA when applying the so-called safety factors. There is however now almost universal agreement that this approach is not scientifically correct. A state of uncertainty may result from a number of factors, such as lack, incomplete or contradictory data. It is not the quantity but the quality of the data that is important. It is possible that an issue that was thought to be scientifically clear to become uncertain as more data become available. When scientific uncertainty is understood in this sense, this cannot be tackled with the application of so-called safety factors or margins, especially for countries that wish to apply a high level of health protection. For example, the genotoxic and carcinogenic potential of oestradiol-17β cannot be adequately addressed by the safety factors applied by JECFA, because the underlying scientific uncertainty about the mechanisms causing cancer are not amenable to quantification so as to be adequately addressed by the safety factors (there is always the risk of under-inclusion). Another example is that when JECFA evaluated the three natural hormones in 1988 and in 1999 and decide not to set a ADI and a MRL, it based its evaluation concerning endogenous production of these hormones by prepubertal children on very old data from 1974 (citing the paper by Angsusingha K. et al: *Unconjugated estrone, estradiol, and FSH and LH in prepubertal and pubertal males and females*, Journal of Clinical Endocrinology and Metabolism, 39: 63-68 (1974), as reported in the 32nd report of JECFA published in the WHO technical report series no 763, page 32). However, the data reported by Angsusingha et al. are no longer valid in view of the more recent findings with more accurate detection and measurement tools available (see the discussion in paras. 121-122 of the EC 2nd written submission in the US panel and the references thereto to the papers by Klein and Klein and by Anderson and Skakkebaek of 1994, 1999 and 2005, respectively).

It follows from the above that the statement by Dr. Boisseau that "for the three natural hormones, oestradiol-17β, progesterone and testosterone, JECFA has decided that the margin of safety deriving from the values of the established ADIs and from a maximum estimated intake of residue was such that it was not necessary to set up MRLs" is plainly wrong. His statement that the European Communities "did not consider any scientific uncertainty" is also false, because a careful reading of

the 1999 risk assessment by the SCVPH shows that the reasons for which that scientific committee considered that oestradiol-17β is a proven carcinogen and that the uncertainty regarding the other five hormones (resulting from the lack of data or the presence of contradictory data) are properly explained and taken into account.

Dr. Boobis also made the equally false statement that: "… the EC assessment of the hormones did not go as far as including some of the considerations for uncertainty used by JECFA because of the conclusion that there was insufficient information to determine whether there was a threshold for the carcinogenic effects. However, for some of the compounds this was based on the results of a small number of non-standard tests of genotoxicity, with equivocal of very weak responses. It is not clear whether the EC applied a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking account the totality of the available data, as was the case by JECFA." Indeed, the three risk assessments of 1999, 2000 and 2002 by the SCVPH did consider the totality of the available data. In fact, Dr. Boobis' reply does not discusses at all that since 2002, the US authorities concluded that "steroidal estrogens are known to be human carcinogens based on sufficient evidence of carcinogenicity in humans, which indicates a causal relationship between exposure to steroidal estrogens and human cancer." For this reason, the US 2002 Report on Carcinogens (RoC) lists steroidal estrogens as known to be human carcinogens with the clarification that this listing now "supersedes the previous listing of specific estrogens in and applies to all chemicals of this steroid class." Moreover, in the same 2002 US Report it is stated 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."[3] So, the 2002 US Report on Carcinogenesis contradicts the allegations made by the US and Canada in these proceedings, which appear to be supported by Dr. Boobis, that the additional burden of residues coming from eating hormone-treated meat is so small that it would make no difference, compared to the level of endogenous production.

Furthermore, neither Dr. Boobis nor Dr. Boisseau mention the fact that the IARC has classified oestradiol-17β in Group 1 as carcinogenic to humans because there is sufficient evidence of carcinogenicity and progesterone and testosterone in Group 2B as possibly carcinogenic to humans. It is therefore a surprising statement by Dr. Boobis that the EC "*did not apply a weight of evidence approach to evaluating the genotoxicity of all of the compounds, taking into account the totality of the available data, as was the case by JECFA*", because it is precisely JECFA's evaluation that is based on old and outdated data and does not examine the totality of the available evidence. Moreover, the argument of Dr. Boobis that a WTO member has to apply a "weight of evidence approach" is legally incorrect. It is not very clear what Dr. Boobis means by this approach, but it must not be taken to mean that only the mainstream scientific views should be accepted or that such an approach could remedy the identified scientific uncertainty. Moreover, this approach would amount to forcing WTO members to dismiss or ignore minority scientific views, which has clearly been rejected by the Appellate Body in the 1998 *Hormones* case, where it held that:

> "Article 5.1 of the SPS Agreement does not require that the risk assessment must necessarily embody only the view of a majority of the relevant scientific community. In some cases, the very existence of divergent views presented by qualified scientists who have investigated the particular issue at hand may indicate a state of scientific uncertainty. In most cases, responsible and representative governments tend to base their legislative and administrative measures on "mainstream" scientific opinion. In other cases, equally responsible and representative governments may act in good faith on the basis of what, at a given time, may be a divergent opinion coming from qualified and respected sources. By itself, this does not necessarily signal the absence of a reasonable relationship between the SPS measure and the risk assessment,

[3] Available at http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540.

> especially where the risk involved is life-threatening in character and is perceived to constitute a clear and imminent threat to public health and safety." (at para. 194 of the AB report)

On a more specific point, Dr. Boisseau is apparently committing the same error as the defending parties because he keeps referring to the "differences in the interpretation of data, as illustrated by the differing conclusions of the CVMP (1999) and the SCVPH (1999)", without knowing that the CVMP has evaluated some of the natural hormones in different preparations and for different purposes (therapeutic or zootechnical use) and its findings are not relevant for the use of the six hormones when administered for animal growth promotion (for which the competence to assess resided with the SCVPH).

C. ASSESSMENT OF OESTRADIOL-17B

Q13. To what extent, in your view, does the EC risk assessment identify the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol-17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice? To what extent does the EC risk assessment evaluate the potential occurrence of these adverse effects?

EC Comments

The European Communities is surprised by the affirmative tone in the statements by Dr. Boisseau and Dr. Boobis that the genotoxic effect of oestradiol-17β is associated with its hormonal activity, when JECFA itself was more cautious when stating that "the carcinogenicity of oestradiol-17β is *most probably* a result of its interaction with hormonal receptors" (emphasis added). Their statements become even more questionable in that they both do not take into account nor do they discuss the most recent and growing scientific evidence linking, directly or indirectly, oestradiol-17β and the other hormones with increased risk of cancer. Unlike what Dr. Boisseau states, there is growing evidence from in vivo studies, (e.g. by Bhat et al., already mentioned above, published in PNAS 100 (2003) 3913-3918) which has shown that estradiol is responsible for both initiation and promotion of tumors *in vivo*. Moreover, carcinogenicity of estrogens is primarily due to oxidative stress/DNA adduct formation caused by the catechols metabolites of estrogens. The role of receptor stimulation is only invoked in the promotion stage of carcinogenesis. For this reason, it is also necessary to consider estradiol-alpha as residues susceptible to be metabolised in consumer in catechol derivative with the same potency as estradiol to give adducts or to induce oxidative stress.

As already explained, it needs to be recalled again that estradiol has been classified as a Group 1 carcinogen by IARC and the results from numerous epidemiological studies support the association of elevated prolonged exposure to endogenous and exogenous estrogen with breast cancer. These studies are supported by studies in experimental animal models that not only include the Syrian hamster kidney model and mouse uterus model, referred to by Dr. Guttenplan in his response to Q. 14, but also the ACI rat (J. Endocrinology, 183, 91-99, 2004) and the ERKO/Wnt mouse (J. Steroid Biochem. Mol. Bio., 86, 477-486, 2003). In both of the latter models a clear dependence of the tumors on estradiol was shown and, in the latter model, the results show that the mammary tumors arise through effects of estradiol not mediated through the estrogen receptor (ER) since the mice lack ER expression.

So there seems now to be agreement that exposure to oestradiol-17β may increase the sensitivity to other carcinogens and thus increase the cancer risk (simultaneous or later in life). One more example

is the ENU-mediated induction of endometrial adenocarcinomas (Takahashi et al., 1996),[4] where simultaneous exposure to oestradiol-17β significantly increased the yield of adenocarcinomas. More recently, the concept of tissue stem cells, as the cells where breast cancer originates, has led to a new concept linking breast cancer risk with the stem cell potential as a measurable variable of the 'fertile soil' for cellular transformation. It is suggested that low-dose estrogen exposure leads to increased proliferation of the tissue stem cells and, since it is hypothesised that the number of potentially carcinogenic tissue stem cells determines the risk of getting the cancer, thereby to an increased risk of breast cancer later in life. This aspect is not at all considered by these experts.[5]

Other adverse effects on human health have also been established. Thus, there are strong data linking administration of very low doses of oestradiol-17β to pre-pubertal girls to changes in growth pattern despite the fact that serum levels of oestradiol-17β remained below the detection limit (Lampit et al., 2002).[6] This may affect the risk for breast cancer later in life because it has been convincingly demonstrated that prepubertal growth rates significantly influence the breast cancer risk (Ahlgren et al., 2004).[7]

The European Communities also disputes the statements by Dr. Boobis that the EC's risk assessment used "speculative assumptions" about misuse or abuse of the product, that no adequate assessment of exposure following use according to GVP was undertaken, or that there was no attempt to estimate the potential occurrence of adverse effects in humans following exposure to levels of the hormones found in meat from treated animals. The experiments conducted by the EC and its findings are based on realistic conditions of use and demonstrate that GVP is frequently not respected in the defending members. The EC exhibits Nos 12, 16, 17, 52, 67, 68, 69 and 73 provide concrete evidence of abuse and misuse of these hormones by the both the US and Canada.

The European Communities agrees with the statement by Dr. Guttenplan that there are basically no direct epidemiological studies comparing matched populations consuming meat from untreated and hormone-treated cattle. However, apart from the ethical concerns, it is difficult to conduct such direct experiments in the presence of so many other confounding factors because of feasibility limitations for observational studies. This being said, it is common that in animal models used in carcinogenesis bioassays (rats and mice) one of the more sensitive tissues for tumorigenesis is liver. At the present time, however, the classification of chemicals as carcinogens does not require that the tumors produced in the bioassays are the same as would appear in humans; chemicals are classified as carcinogens when they cause a significant increase in tumors regardless of the tissue.

Q14. In your view, does the risk assessment undertaken by the European Communities on oestradiol-17β follow the Codex Guidelines on risk assessment, including the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization with respect to oestradiol-17β?

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[4] See Takahashi M, Iijima T, Suzuki K, Ando-Lu J, Yoshida M, Kitamura T, Nishiyama K, Miyajima K, Maekawa A.: Rapid and high yield induction of endometrial adenocarcinomas in CD-1 mice by a single intrauterine administration of N-ethyl-N-nitrosourea combined with chronic 17 beta-estradiol treatment, in Cancer Lett. 104:7-12 (1996).

[5] *See* Smalley M., Ashworth A.: *Stem cells and breast cancer: A field in transit*. Nat Rev. Cancer. 2003, 3(11) :832-44, and Baik I., Becker P.S., DeVito W.J., Lagiou P., Ballen K., Quesenberry P.J., Hsieh C-C.: *Stem cells and prenatal origin of breast cancer*. Cancer Causes and Control 15: 517–530 (2004).

[6] *See* Lampit M., Golander A., Guttmann H., Hochberg Z.: *Estrogen Mini-Dose Replacement during GnRH Agonist Therapy in Central Precocious Puberty: A Pilot Study*. The Journal of Clinical Endocrinology & Metabolism 87:687–690 (2002).

[7] *See* Ahlgren M., Melbye M., Wohlfahrt J., Sorensen T.I.: *Growth patterns and the risk of breast cancer in women*. N. Engl. J. Med. 351:1619-26 (2004).

EC Comments

The European Communities disagrees with the statement by Dr. Boobis because from a careful reading of the 1999, 2000 and 2002 risk assessment by the SCVPH it is obvious that it has followed the four steps of risk assessment when it carried out its qualitative risk assessment. That this is so is also confirmed by the statement by Dr. Boisseau although Dr. Guttenplan gives it a "mixed rating" in following the Codex guidelines which became available in 2003.

For the sake of completeness, however, it should also be clarified that Dr. Guttenplan has not considered the studies on the ACI rat and ERKO/Wnt mouse. The studies carried in experimental animal models do not only include the Syrian hamster kidney model and mouse uterus model, referred to by Dr. Guttenplan, but also the ACI rat (J. Endocrinology, 183, 91-99, 2004) and the ERKO/Wnt mouse (J. Steroid Biochem. Mol. Bio., 86, 477-486, 2003). In both of the latter models a clear dependence of the tumors on estradiol was shown and, in the latter model, the results show that the mammary tumors arise through effects of estradiol not mediated through the estrogen receptor (ER) since the mice lack ER expression. In addition, there are several additional models in transgenic mice where mammary tumor formation has been shown to be estrogen dependent.

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

Q15. Does the identification of oestradiol-17β as a human carcinogen indicate that there are potential adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes? Does your answer depend on whether good veterinary practices are followed? [see para. 206-207 of EC Rebuttal Submission (US case), para. 121 of EC Rebuttal Submission (Canada case), paras. 97-98 of EC Replies to Panel Questions, paras. 76-77, 150 and 155-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission]

EC Comments

The European Communities notes the different and in some parts contradictory statements by the four experts that replied to this question. It agrees with the reply of Dr. Cogliano. It also agrees that if GVP is not followed, the risk is even higher. For the benefit of Dr. Guttenplan, the EC would clarify that the term "potential" in the SPS Agreement has indeed been interpreted by the Appellate Body in the 1998 *Hormones* case to mean "possible" (at para. 185 of the report).

The position of Dr. Boobis and that of Dr. Boisseau is conditioned by their understanding that oestradiol-17β is causing cancer only through receptor mediated processes. This hypothesis is however scientifically no longer tenable in light of more recent evidence cited by the European Communities. Reading between the lines of their replies, however, these two experts also do not seem to deny completely the existence of possible adverse effects from residues in meat from animals treated with this hormone for growth promotion purposes.

Q16. Does the scientific evidence relied upon in the SCVPH Opinions support the conclusion that carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity? [see para. 148 of the EC Replies to Panel Questions and paras. 35-40 and 46 of US Rebuttal Submission]

EC Comments

The European Communities disagrees with the statements of Dr. Boisseau and Dr. Boobis. For Dr. Boisseau there is only one other authoritative source of comparison, that is the JECFA reports, irrespective of the outdated nature of its reports and old data on which they are based. In his long reply, Dr. Boisseau interprets lack of data as lack of adverse effects. Is this really a valid approach that is followed by JECFA? Dr. Boisseau further criticises the SCVPH assessments on the ground that they did not include a "quantitative assessment" of the risk or that it did not establish its genotoxicity with data from experiments *in vivo*. Dr. Boisseau does not probably know that the Appellate Body has held that a *qualitative* assessment of risk is acceptable for the purposes of the *SPS Agreement*. Moreover, he does not consider the other more recent evidence cited by the European Communities showing the direct genotoxic potential of oestradiol-17β, progesterone, zeranol and most possible testosterone. As regards MGA and trenbolone acetate the evidence may be inconclusive but there are sufficient indications to treat them as such, despite the serious gaps in our scientific knowledge.

Amongst the flaws in Dr. Boobis' reply is that he criticises the EC assessment for not having evaluated these hormones "on a weight of evidence" basis. However, this type of criticism is scientifically inaccurate and legally inappropriate for the purposes of the *SPS Agreement* for the reasons explained in the EC's comments on the reply to question no 12 above. Moreover, he states that "*JECFA concluded that whilst oestradiol is a human carcinogen, its mode of action is such that there would be no appreciable risk of cancer at exposures up to the ADI*". JECFA's statement that there is no appreciable risk is a subjective expression, but it does confirm that there is excess risk due to added hormone. Again, "appreciable risk" is a qualitative and not a quantitative term, and thus fails to provide the necessary assurance that the EC's level of protection of no risk from residues of these hormones in meat will be achieved.

Dr. Guttenplan makes a more informed assessment of the scientific situation and concludes that the more recent evidence cited by the European Communities does support the finding that the genotoxic action of these hormones is not related only to their hormonal activity. Indeed, Dr. Guttenplan acknowledges that the evidence is now sufficient to support a role for the estrogen metabolites which include the genotoxic, mutagenic estrogen quinones in estrogen carcinogenicity (New Eng. J. Med., 354, 270-282, 2006).

Q17. Could you comment on Canada's statement that "the studies commissioned by the European Communities also failed to find evidence of "catechol metabolites" – that is the oestradiol metabolites identified as the source of the genotoxic potential – in meat from treated animals"? What would be the implication of an absence or presence of catechol metabolites? [see para. 102 of Canada Rebuttal submission, EC Exhibit 51A]

EC Comments

The European Communities agrees with the statements by Dr. Guttenplan and Dr. Cogliano. Indeed, it is known that, in contrast to humans, cattle do not efficiently metabolize estradiol to catechols and this apparently explains the very low levels of catechols in meat. Furthermore, the real problem is not to prove the presence of catechols as residues in edible tissues, but to determine the real part of estradiol, estradiol-alpha or estrone that will be metabolised in catechols in target tissues. Due to their structure, catechols metabolites eventually found as residues in edible tissue of treated cattle would exist more probably as glutathione conjugates and only a small part of them as glucuronides. Nevertheless, due to their chemical reactivity, catechols as such are not stable enough because they are already transformed in a more stable form. Therefore, more worrying from the human health point of view is the part of estrogens (estradiol, estradiol-alpha or estrone) which will be metabolised in catechol derivatives in target tissues. This is the reason for which it is necessary to perform a complete residue analysis with

more powerful detection methods. Thus, as Dr. Guttenplan correctly states, the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity.

Indeed, it is important to keep in mind that in the ACI rat, mammary tumors were not induced by the administration of the catechol metabolites of estradiol, but only by administration of estradiol. Furthermore, the fact that exposure to the catechol metabolites does not cause mammary tumorigenesis does not necessarily negate the possibility that the catechol metabolites formed in mammary tissue play a role in mammary tumorigenesis. This is because administered metabolites may not reach levels in mammary tissue comparable to those achieved by metabolism of estradiol to the catechols within the mammary tissue itself. Analysis of both human and mouse mammary tissue has demonstrated the presence of catechol metabolites and conjugates of estrogen quinones with glutathione, the latter demonstrating that oxidative metabolism of estradiol to the catechols and their further oxidative metabolism to reactive estrogen quinones occurs in normal human and mouse mammary tissue (Carcinogenesis, 22, 1573-1576, 2001; Carcinogenesis, 24, 697-702, 2003).

As regards the statements by Dr. Boisseau and Dr. Boobis, they can only be explained by their lack of specific expertise on these hormones, as they have not carried any specific research on these substances in their professional life. Their statements therefore should carry no weight. Indeed, it should be recalled that during the 1997 panel report on hormones, one of the experts for the panel (Dr. G. Lucier) had stated:

> "For every million women alive in the United States, Canada, Europe today, about a 110,000 of those women will get breast cancer. This is obviously a tremendous public health issue. Of those 110,000 women get breast cancer, maybe several thousand of them are related to the total intake of exogenous oestrogens from every source, including eggs, meat, phyto-oestrogens, fungal oestrogens, the whole body burden of exogenous oestrogens. And by my estimates one of those 110,000 would come from eating meat containing oestrogens as a growth promoter, if used as prescribed."

However, the Appellate Body in 1998 denied evidentiary value to Dr. Lucier's statement for the reason that his opinion "… does not purport to be the result of scientific studies carried out by him or under his supervision focusing specifically on residues of hormones in meat from cattle fattened with such hormones …". (at para. 198 of the 1998 Appellate Body report)

In this case, Dr. Boisseau has explicitly admitted that he has never carried any experiments on hormones and has published no scientific paper, and the same applies for Dr. Boobis who does not appear to have any publication on hormones either.

Q18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol-17β is genotoxic. Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see paras. 118-119 of EC Rebuttal Submission (US case), paras. 123-124 of EC Rebuttal Submission (Canada case), paras. 87-91 and 153-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission, and paras. 90-97 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with the statements by Dr. Guttenplan and Dr. Cogliano. The evidence both *in vitro* and *in vivo* was already strong at the time of adopting the EC Directive and it is even stronger now establishing the direct genotoxic action of oestradiol-17β. In support of Dr. Guttenplan's statement that the evidence for the genotoxicity of estradiol is now stronger, see *New Eng. J. Med., 354, 270-282, 2006.*

The question is not whether the European Communities has established that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans, but whether the US and Canada have demonstrated to the requisite standard of proof that this adverse effect would not occur. They both assume (as does JECFA) that it will not occur, but they have failed to prove it, as has correctly been pointed out by Dr. Cogliano. As mentioned above, in the ACI rat model, the catechol estrogens did not cause mammary tumors; however, estradiol did cause such tumors in a dose-dependent response. Assuming greater bioavailability of estradiol and the fact that its oxidative metabolism to catechols and quinones occurs in various tissues as documented by their detection, the conclusion stated by Dr. Guttenplan that their absence in meat does not imply that meat from estrogen-treated cattle is without risk is correct.

The statement by Dr. Boisseau is beside the point, since the argument is hardly convincing that in 1999 JECFA established for the first time an ADI "in order to present in a more convincing way the outcome of its assessment". There is no trace of such an argument in the 1999 JECFA report which, it should be recalled, had found for the first time that "oestradiol-17β has genotoxic potential" (this admission was not in its 1988 report). Equally, the statement by Dr. Boobis lacks conviction because it is cast in cautious/conditional terms ("some, if not all, of the genotoxicity observed in vitro *would be expected* to exhibit a threshold…"). Again, Dr. Boobis appears to disregard the fact that evidence *in vivo* existed at the time that showed the direct genotoxicity of oestradiol-17β, which is reported in the 1999 SCVPH assessment and in the EC submissions to this Panel.

Q19. The European Communities states that "...it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance". Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case),paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]

EC Comments

The European Communities agrees with the thrust of the statements by Dr. Cogliano and Dr. Guttenplan. Indeed, it is true that there is no reason to expect a threshold to exist for a genotoxic chemical. After all, whether cancer will occur as a result of genotoxicity or hormonal action is from the regulatory point of view less critical, as the end result is the same: human cancer. As Dr. Guttenplan has stated, although DNA repair can occur, it presumably is occurring at all doses and the fraction of DNA damage repaired probably does not change at physiological levels, because the repair enzymes are unlikely to be saturated. However, would it not also be true that if the rate of repair were constant, an increase in the rate of formation of DNA damage would result in an increase in the time a mutagenic lesion remained in DNA? If this were the case, then there would be an increased likelihood for mutation if cell proliferation were occurring.

The arguments of Dr. Boisseau and Dr. Boobis that there is "no good evidence" that oestradiol is genotoxic *in vivo* or that it causes cancer by a genotoxic mechanism are unfounded. There are also a number of papers showing *in vivo* genotoxicity, some of which are already mentioned in the 1999 SCVPH report. Moreover, there are a number of scientific papers linking clearly elevated levels of 17β-oestradiol and other estrogens, at specific timepoints during development, to increased cancer risk (e.g. Hilakivi-Clarke L., Cho E., Raygada M., Kenney N.: *Alterations in mammary gland*

development following neonatal exposure to estradiol, transforming growth factor alpha, and estrogen receptor antagonist ICI 182,780, in J. Cell Physiol. 1997 170:279-89). The levels of 17β-oestradiol in children are so low that Dr. Boisseau's statement cannot be accepted scientifically. In the EC's view, it is beyond doubt that there is a link between 17β-oestradiol exposure during development (pre- and post-natal) and the risk of breast cancer later in life and this is not only due to endogenous production.

Q20. In your view, how do the European Communities' conclusions above relate to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary"? To what extent, in your view, has JECFA's conclusion that oestradiol "has genotoxic potential" affected its recommendations on this hormone?

EC Comments

The European Communities notes that Dr. Boobis, after so many assumptions and hypothesis in his reasoning of which he offers no proof, arrives at the conclusion that:

> "… a modest incremental increase in oestradiol concentration from exogenous exposure (above the ADI) might conceivably perturb endocrine effects, depending on the physiological state. However, non-endocrine effects, such as genotoxicity, will depend on the circulating concentration of oestradiol and will not vary with physiological state. Hence, the natural variations in circulating oestradiol levels should have a much greater effect on any genotoxic response than the much more modest change that could arise from the hormone in meat from treated animals, at any conceivable level arising from its use as a growth promoter …".

This reply of Dr. Boobis is based on his more erroneous underlying assumptions that oestradiol-17β is not genotoxic, that there is a threshold for residues in meat from animals treated with this hormone for growth promotion purposes, and that the rate of endogenous production by prepubertal children is as stated in the JECFA report. If these assumptions are false, as the available scientific evidence clearly demonstrates, then Dr. Boobis' statement – which is already a qualified one - would make no sense.

In any case, for the information of Dr. Boisseau and Dr. Boobis, the European Communities recalls that in the 1997 WTO hormones panel report (i.e. the first hormones panel), the US, Canada and JECFA were arguing that oestradiol-17β is not genotoxic, and this had influenced the findings of the 1987 panel report on these hormones. Since then, as the European Communities has been consistently arguing, the genotoxicity of oestradiol-17β is no longer seriously disputed and has now for the first time been accepted and written in the 1999 JECFA report re-evaluating the three natural hormones. But JECFA was not at all sure whether the genotoxicity of oestradiol-17β is due to its receptor-mediated action or by other direct mechanisms, because it uses in its 1999 report the soft terms "the carcinogenicity of oestradiol-17β is *most probably* a result of its interaction with hormonal receptors" (emphasis added). This contrasts sharply with the more affirmative and assertive statements to the contrary by both Dr. Boisseau and Dr. Boobis, who, by the way, have not done any direct experiments on these hormones in their professional life and so lack specific expertise.

More importantly, as the Appellate Body has held in the 1998 *Hormones* report:

> "… in most cases, responsible and representative governments tend to base their legislative and administrative measures on "mainstream" scientific opinion. In other cases, equally responsible and representative governments may act in good faith on the basis of what, at a given time, may be a divergent opinion coming from qualified

> and respected sources. By itself, this does not necessarily signal the absence of a reasonable relationship between the SPS measure and the risk assessment, especially where the risk involved is life-threatening in character and is perceived to constitute a clear and imminent threat to public health and safety…".

Indeed, in this case Dr. Boobis is basing his arguments on so many assumptions and hypothesis in order to arrive at the conclusion that oestradiol-17β is genotoxic only through its hormonal activity; but can Dr. Boobis provide the necessary assurance to the responsible risk management authorities of the EC that the residues of these hormones in meat from animals treated for growth promotion will not increase the risk of cancer? Furthermore, can Dr. Boobis clarify whether he believes that the evidence on which the EC based its risk assessment on genotoxicity of oestradiol does not come from "qualified and respected sources"?

It is also noteworthy that Dr. Boobis does not comment on other relevant evidence, for instance the fact that the US authorities also concluded for the first time in 2002 that "steroidal estrogens are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans, which indicates a causal relationship between exposure to steroidal estrogens and human cancer." For this reason, the US 2002 Report on Carcinogens (RoC) lists steroidal estrogens as known to be human carcinogens with the clarification that this listing now "supersedes the previous listing of specific estrogens in and applies to all chemicals of this steroid class." Moreover, in the same 2002 US Report it is stated 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."[8]

Dr. Boisseau and Dr. Boobis consider the assessments of JECFA as the Bible, although they know that the 1988 and the 1999 JECFA assessments are outdated by today's evidence and scientific standards. The European Communities has asked JECFA back in 1998 to withhold for a couple of years its assessment in order to take into account the new evidence which was then going to become available soon as a result of the studies that have been commissioned by the European Communities following the 1998 Appellate Body report in hormones. But JECFA for unknown reasons decided not to wait, despite the lack of any kind of urgency to review the three natural hormones in 1999. The European Communities hopes that JECFA will carry soon another assessment of these hormones on the basis of the most recent evidence available.

The European Communities agrees with the statements of Dr. Cogliano and Dr. Guttenplan. Indeed, the European Communities is arguing that a threshold cannot be established for the incremental human exposures that would be found in meat residues because there can be no assurance – and the US, Canada and JECFA did not provide one - that these additional exposures may not increase cancer risk, especially for the most sensitive parts of the population (prepubertal children), taking also into account the other identified areas of concern, such as developmental effects.

Q21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential? Does your answer depend on whether good veterinary practices are followed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see, *inter alia*, the SCVPH Opinions and paras. 63, 83, 89-91 and 93 of US First Submission, paras. 131-136 of Canada Rebuttal Submission]

EC Comments

[8] Available at http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540.

The European Communities is puzzled by the dismissive statements by Dr. Boisseau and Dr. Boobis. It is noteworthy that the 1999 JECFA report, on which they so much rely, states that *"... equivocal results have been reported for the induction of single-strand DNA breaks and DNA adducts have been seen in vivo and in vitro in some studies…*" (see WHO, technical series report no 893, at page 61). Because it is said that progesterone is not found to be mutagenic, JECFA concluded that "*on balance, progesterone has no genotoxic potential*" (emphasis added). It is recalled that no such statement was available in the 1988 JECFA evaluation report on this hormone. So, unlike Dr. Boisseau and Dr. Boobis, JECFA was more prudent when rejecting the genotoxicity of progesterone in 1999. Since then, more evidence has become available, as explained in the submissions of the European Communities, which increases the likelihood of possible genotoxic effects of progesterone and the other hormones. The 1999, 2000 and 2002 risk assessment by the SCVPH provide enough evidence to demonstrate that genotoxicity and other adverse effects from these hormones are possible and that there are a number of uncertainties surrounding their mechanism of action to warrant further investigation. As Dr. Guttenplan states, their genotoxic potential may be weak but cannot be excluded. In particular, the evidence available to the US, Canada and JECFA on the basis of which these hormones were authorised for animal growth promotion purposes, which dates in most of these hormones since the 1970s, is today not complete nor adequate to respond, with the required degree of certainty, to the gaps in our scientific knowledge which have been clearly identified in the 1999 and 2002 evaluations by the SCVPH. It should also be recalled that the European Communities did not permanently prohibit these hormones as proven carcinogens, as it did with regard to oestradiol 17β, but on a provisional basis taking into account the numerous and serious gaps in our scientific knowledge which have been clearly identified in the SCVPH assessments. The relevant question therefore is whether these two scientists, who – it should be recalled have no specific expertise on hormones - contest that there exists at least some uncertainty regarding the genotoxicity and other possible risks from the residues of these hormones in meat that have been identified by the SCVPH?

As regards the respect or not of good veterinary practice, the increased presence of these hormones in meat from cattle presumably treated with preparations containing these hormones has the potential to affect the hormone levels, in particular in infants and prepubertal children, whose levels of serum are much lower than those used by JECFA, as the more sensitive RCBA assays now demonstrate.

Q22. How would you define *in vivo* DNA repair mechanisms? How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat? Does your answer depend on whether good veterinary practices are followed in the administration of these hormones? To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones? Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why? [see para. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission].

EC Comments

Dr. Boobis's reply summarises more or less accurately the difficulties authorities face with genotoxic substances by stating that: "…A major difficulty in the risk assessment of such compounds however, is the identification of the threshold for such effects. This is because they occur with low incidence, and experimental studies do not have the statistical power to determine the location of the threshold with any confidence. Thus, whilst recognizing the likelihood for a threshold for even genotoxic effects the risk assessor is faced with the impossibility of locating it. The conservative solution is to assume that the response is linear and that there is no dose below which exposure is safe." (references omitted) Dr. Boobis then goes on to deny direct genotoxic potential to residues in meat from these hormones. However, if his underlying assumptions concerning lack of direct genotoxicity are false,

i.e. that oestradiol-17β is genotoxic and that there is no threshold for residues in meat from animals treated with this hormone for growth promotion purposes and that the rate of endogenous production by prepubertal children are much lower than those stated in the JECFA report, then Dr. Boobis should accept that DNA repair mechanisms are not sufficient to eliminate DNA damage.

Moreover, Dr. Boobis and Dr. Guttenplan appear to miss another important point. If the rate of repair were constant, an increase in the rate of formation of DNA damage would result in an increase in the time a mutagenic lesion remained in DNA. If this is the case, then there would be an increased likelihood for mutation if cell proliferation were occurring. Dr. Guttenplan states that "…most DNA damage by any agent is repaired and there is considerable redundancy in DNA repair, insuring that repair is effective. However, a small fraction of damage inevitably escapes repair …". The implication of this should be that the unrepaired fraction would be increased with an increase in the rate of damage formation resulting from increased exposure to estradiol and the resulting estrogen genotoxic metabolites. In other words, a higher rate of damage may be accompanied by an increased fraction of unrepaired potentially mutagenic lesions.

The European Communities notes also the interesting statements by Dr. Guttenplan that "… there is no reason to assume that DNA repair processes involved in DNA damage produced by estrogen metabolites are any more or less effective than those involved in repair of other carcinogens …", and that "… since it is not likely to be different for estrogen derived damage than other types of damage it is not really relevant [if this is not examined in detail by the SCVPH]. There is some evidence referred to in the SCVPH Opinions that error-prone DNA repair of certain estrogen derived damage can occur."

Q23. To what extent is it necessary or possible to take into account the "long latency period" of cancer in the conduct of a risk assessment, which is supposed to assess carcinogenic effects of these hormones when consumed in meat? Have the hormones in dispute been used as growth promoters over a sufficient number of years for an assessment of their long-term effects on human health to be made? [see para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case)].

EC Comments

The European Communities notes the different and partly contradictory replies of the experts. It agrees, however, with Dr. Cogliano and Dr. Guttenplan that a sufficiently long latency period (at least 20 years) is extremely important. However, it is also true that such epidemiological studies will not be able to discriminate (or separate out) the true origin of cancer because of so many co-founding factors. This is admitted by both Dr. Boisseau and Dr. Boobis, thus undermining the position of the US and Canada that these hormones have been in use for a long time to be able to rule out their carcinogenic effects on humans. And Dr. Boobis concludes by stating that "…Hence, a negative result from such an observational study would not resolve the issue." However, the European Communities would recall the evidence cited in the 1999 SCVPH report – coming from the studies published by the IARC – showing that the frequency of breast cancer in countries where hormones are allowed is higher compared with countries where the hormones have not been used. Thus, this is just an indication that there might be a link between consumption of red meat and breast cancer.

Q24. To what extent is it possible to identify possible confounding factors causing cancer and attribute them to identified sources? What are the implications of these factors for the conduct of a risk assessment evaluating the adverse affects caused by residues of growth promoting hormones in meat? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

EC Comments

The European Communities notes that the replies of all the scientists substantially agree with the EC position and the reasons for which it was not possible to carry out such an epidemiological study after the 1998 Appellate Body report in the hormones case. Moreover, their replies also undermine indirectly the position of the US and Canada that these hormones have been in use for a long time to be able to identify and, hence, rule out their carcinogenic effects on humans. However, the European Communities would recall the evidence cited in the 1999 SCVPH report – coming from the studies published by the IARC – showing that the frequency of breast cancer in countries where hormones are allowed is higher compared with countries where the hormones have not been used. This is of course no conclusive proof, but just an indication sufficient to raise concerns about the gaps of our knowledge in this area.

Q25. To what extent do the three recent studies referred to by the European Communities confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones? Please also comment on the EC statement that one of the studies "was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, which means that the subjects should have been exposed to hormone-free meat in their diet. This may further imply that it cannot be excluded that the risk of cancer may be further increased if meat treated with hormones for animal growth promotion were to be consumed". [see paras. 145-148 of EC Rebuttal Submission (US case) and paras. 139-142 of EC Rebuttal Submission (Canada case), footnote 97 in para. 147 of EC Rebuttal Submission (US case), and Exhibits EC-71,72,73]

EC Comments

The European Communities notes the different and partly contradictory views expressed by the experts. Dr. Boobis dismisses the relevance of the studies cited by the European Communities for reasons that have to do essentially with what he calls the "weight of the evidence" approach. But as the European Communities explained before, this approach is not appropriate nor is it required under the *SPS Agreement*. It appears that Dr. Boobis' strongly held views - which it is worth recalling do not come from specific research he has conducted himself on these hormones - would only change if the evidence produced by the European Communities "confirms a risk to human health". Dr. Boobis is apparently not restrained in displaying such strongly held views, despite the fact that JECFA's evaluation is based on data from the 1970s – 1980s, when the experiments conducted by the industry then seeking regulatory approval in the US did not comply either with the kind of criticism now levelled by Dr. Boobis against the more recent evidence produced by the European Communities. In other words, Dr. Boobis is now demanding evidence of positive proof of harm, which the applicant pharmaceutical industry did not disprove (i.e. the lack of possible harm) with the data it submitted for regulatory approval in the 1970s and 1980s in the US.

Dr. Boobis apparently feels no restrain as an expert to state that: "*as long as exposure does not consistently exceed the ADI, there should be no appreciable risk to human health*." But this is both speculative and unspecific. What is an appreciable risk? How do we interpret the qualitative term "no appreciable risk"? Is it 1% or 10% or some other value? And why would a scientific expert, who is supposed to do only a risk assessment, decide what is "appreciable" risk, a task reserved normally for the risk manager? Is it not normally the task of a scientific expert in a risk assessment exercise to explain the scientific evidence and see if there is scientific uncertainty? How confident can Dr. Boobis be when stating that: "However, as indicated elsewhere in my responses, the evidence is against an increased risk from such exposures". Would Dr. Boobis accept that there is some uncertainty surrounding his statements rejecting an increased risk of cancer from the residues of these hormones in meat? And would Dr. Boobis contest that the evidence with which he does not agree comes from reliable and credible sources?

Another example of the "absolutist" approach by Dr. Boobis is his comment on the EC epidemiological study making a correlation between meat consumption and colorectal cancer, showing an increased frequency in the US and Australia compared to Europe. But he dismisses these results because he relates the lower risk observed in Europe by linking it with a lower meat consumption in Europe. However, the numbers showing a lower frequency of colorectal cancer is only from Northern Europe, whereas the data for meat consumption is for all European countries combined. If so, would Dr. Boobis accept that this data might indicate that some uncertainty exists concerning the alleged by the US and Canada safety of hormone residues in meat treated for animal growth promotion?

The European Communities agrees with the comments of Dr. Cogliano, who rightly summarises the issues at stake. The European Communities also agrees with the careful and scientifically sound statement by Dr. Guttenplan concerning the study by *Liu S and Lin YC (2004)*, in that their "... observation was not previously reported …" and that "… the study does suggest that additional tests of zeranol should be carried out." Consequently, the relevant legal question is who is to conduct these additional experiments and what should the regulatory regime be until their results become available? One of provisionally prohibiting or one of allowing the use of these hormones for growth promotion purposes?

Q26. Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91]

EC Comments

The European Communities notes the different views expressed by the experts. What is important, however, is that there appears to be some consensus for the proposition – nicely summarised by Dr. Cogliano – that: "… *it is possible that differences in exposure to exogenous hormones can be one cause, but the data are not sufficiently specific to establish a link between these observations*." Indeed, Dr. Boobis also states 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. There are some studies that are consistent with such an association, but there are several other possible explanations for the findings, some of which are more plausible than hormones in meat as being causal.*." (emphasis added). And Dr. Guttenplan states that: "… *However, the results are at least consistent with a possible effect of hormones on breast and prostate cancer ...*".

As already explained above, their replies undermine indirectly the position of the US and Canada that these hormones have been in use for a long time to be able to identify and, hence, rule out their carcinogenic effects on humans. It should also be pointed out that the European Communities cited this epidemiological evidence in the 1999 SCVPH not as an affirmative or adequate proof but just as an indication and possible explanation. In this sense, the three experts appear to agree, although at varying degrees. Furthermore, the plausibility of the EC argument is slightly reinforced by the fact that the differences in the cancer rates observed in the European Communities and US go in the expected direction in case of an effect, with higher rates in places where hormone-treated meat is consumed; and, similarly, the study of time trends is in agreement with the use patterns of these products in animal production. Again, the European Communities advanced this argument to demonstrate that the scientific uncertainty is growing concerning the harmless nature of the residues

of these hormones in meat and to counter the arguments of the US and Canada that there is no uncertainty surrounding the safety of residues of these hormones.

(b) Residue analysis

Q27. How do the residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue?

EC Comments

The European Communities wishes to stress that the difference in the residues is not only structural/chemical but also qualitative and quantitative. For instance, one of the studies by the EC (Stephany 2001, APMIS 109, 357-364) (see exhibits EC-49 and EC-19) gives some data on residues in meat samples from the US market. In the so called "HQ clean HFC US beef" study (i.e. hormone-free meat), an average 0.004 ppb of estradiol was found, whereas in the so called "M/LQ domestic US beef" study (i.e. hormone-treated beef) an average of 0.030 ppb estradiol was present. So this study indicates that the consumption of meat from the regular US market contains *7.5 times more estrogens than in meat from untreated cattle.* This is important and completely different information from that provided in the data from the controlled studies which were conducted in the 1960s, 1970s and 1980s by the pharmaceutical industry for the purpose of seeking authorisation of these hormones in the US and Canada (and on which JECFA based its evaluations in 1988 and in 1999).

Q28. How do the hormones naturally present in animals, meat, or human beings differ from the residues in meat of the three natural hormones used for growth promotion purposes?

EC Comments

The European Communities would note that the statement by Dr. Boisseau is partially incomplete and partially false. First, no estradiol-alpha is produced endogenously by humans, whereas this is the main residue in the target tissue (liver) in cattle treated with oestradiol 17β. This metabolite, when ingested by humans, is highly susceptible to give catechols in target organs (colon, liver) which may react with nucleophilic compounds and induce some disruptions. Moreover, the hormonal effect of estradiol-esters which are found as residues in treated cattle are not examined in the old data submitted by the pharmaceutical industry for the approval of this hormone, despite the fact that we know that they are orally active and probably partially absorbed in the intestine lymph circulation.

The European Communities considers the statement by Dr. De Brabander very informative, in particular the statements the three natural hormones used for growth promotion purposes are synthetised (prepared) from plant material and that in plant material the $^{13}C/^{12}C$ ratio is different from the $^{13}C/^{12}C$ ratio of animals. Equally, the finding that the residues of the endogenously produced natural hormones in cattle are in the 17α form (inactive) while the use of the natural hormones for growth promotion purposes may lead to residues in the ß form (active form). The first of these remarks may provide a better understanding to the simplistic argument made by the US and Canada that humans are exposed to much higher burdens of residues from these hormones when eating natural products (e.g. broccoli) and they should not worry about the little increment they receive from eating meat treated with these hormones for animal growth promotion purposes.

Q29. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the synthetic hormones found in meat in their assessment of the risks from such residues? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? How do they compare with the MRLs set by Codex? [see paras. 165-176 of EC Rebuttal Submission (US case); pages 55-68 of the Opinion of the SCVPH

of 30 April 1999 in US Exhibit 4, para. 144 of US First Submission, Exhibits US-6 and 7, footnote 46 of US Rebuttal Submission]

EC Comments

The European Communities considers that the statement of Dr. Boisseau is incorrect because the 1999 opinion of the SCVPH was structured in two levels: one making the analysis stated by Dr. Boisseau, but also a second one where an exposure assessment was nevertheless made to residues of the synthetic hormones (trenbolone, zeranol and MGA) in meat, in particular to underscore the point that the ADIs fixed by JECFA are most likely to be exceeded as regards specifically prepubertal children, taking into account their low levels of endogenous production. Specific reference can be made to paras. 165-176 of the EC's rebuttal submission and to the clearly marked sections of the 1999 SCVPH opinion. The European Communities not only considered the ADIs and MRLs set by JECFA but went even further and examined the tolerance levels recommended by the USA. Moreover, it is obvious, even from a cursory look at the 1999 and 2002 SCVPH opinions, as well as from the Exhibits EC-65, 67, 68, 69, 70 and 73, that the European Communities did examine the consequences from observance or lack thereof of GVP.

The statement by Dr. De Brabander confirms the EC argument that the data used by JECFA are not only too old but have also been obtained with methods that are no longer reliable today. This may also explain why the parties and JECFA have so strongly refused to provide those data to the European Communities and the Panel.

Q30. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the three natural hormones in meat in their assessment of the risks from such residues? Is it possible to compare these to the ADIs recommended by JECFA in 1999? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? [see paras. 120-123 and 155-164 of EC Rebuttal Submission (US case), pages 33-54 of 1999 Opinion in Exhibit US-4, para. 144 of US First Submission, and 52nd JECFA Report in Exhibit US-5]

EC Comments

For the reasons already explained above regarding the synthetic hormones, the European Communities considers that the statement of Dr. Boisseau is also incorrect as regards the three natural hormones. Specific reference can be made to paras. 155-164 of the EC's rebuttal submission and to the clearly marked sections of the 1999 SCVPH opinion. The European Communities not only considered the ADIs and MRLs set by JECFA but went even further and examined the acceptable levels and tolerances recommended by the USA. Moreover, it is obvious, even from a cursory look at the 1999 and 2002 SCVPH opinions, as well as from the exhibits EC-65, 67, 68, 69, 70 and 73, that the European Communities did examine the consequences from observance or lack thereof of GVP.

The European Communities considers that the statement by Dr. Boobis is clearly wrong. In section 4.1.5 of the 1999 opinion, the SCVPH made a detailed exposure assessment both for the ADI established by JECFA and the acceptable levels and tolerance recommended by the US authorities. It is recalled that JECFA did not recommend MRLs for the different types of tissue, while the US has identified acceptable levels. Therefore, for comparative purposes and in order to be exhaustive, the SCVPH had to apply conversion rates. The result was that the ADI recommended by JECFA (0-50 ng/kg bw/day) is lower than that recommended by the US (102 ng/kg), as calculated by the SCVPH on the basis of the acceptable levels for individual tissues. However, both the JECFA and the US values are based on endogenous production by prepubertal children that the SCVPH found to be too high.

As the SCVPH found that the US acceptable levels and recommended tolerance will be exceeded by about 1,700 fold times, it was obvious that the JECFA ADI, which is lower than the recommended US tolerance, will also be necessarily exceeded. The SCVPH exposure assessment is made for prepubertal children, as the most sensitive part of the population. Moreover, the data used in section 4.1.5 of the 1999 SCVPH report are based on residue values that are assumed to result from administration of these hormones that respects use as authorised in the US ("GVP"). Indeed, Table A3 attached as Annex to the 1999 opinion uses the TMDI from the 1999 JECFA report. There is another section in the 1999 SCVPH opinion (section 3.3), which discussed the higher residue values that will result inevitably from misuse and abuse. It should also be added, that the same methodology and reasoning was applied for the other 2 natural hormones.

While it is admitted that an exposure assessment on natural hormones is a difficult task that has to cope with many uncertainties and may therefore not be as straightforward as desired, Dr. Boobis opinion that the European Communities did not carry out an appropriate exposure assessment is clearly not justified.

Q31. Please comment on the US statement that "concentrations of oestradiol-17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of oestradiol-17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." In your reply please take into account the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels" and the statement by the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered. [see paras. 51 and 144 of US First Submission and Exhibits US-6 and 7, para. 98 of EC Replies to Panel Questions, Exhibit EC-101, and paras. 2.3.2.3 of the 1999 Report of SCVPH]

EC Comments

The European Communities considers that Dr. Boisseau's reply accepts the US statement without much questioning. However, in the US statement there exist phrases which are imprecise and possibly misleading, such a "… do not vary significantly …", "… well within the physiological range …", "… may be slightly higher …". Neither the US nor Dr. Boisseau explain what is significant or what is the physiological range, as we know that the values for these concepts can vary substantially. For example, as explained by Dr. De Brabander in his reply to question no 27, one of the studies conducted by the European Communities indicates that the consumption of meat from the regular hormone treated meat market in the US contains 7.5 times more estrogens than in meat from untreated cattle. Moreover, Dr. Boisseau did not comment on the part of the question relating to the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels." Indeed, in this 11th US report the terms "can increase estrogens in tissues of food producing animals to above their normal levels" do not explain by how much above their normal levels – supposing one could define such normal levels – could such an increase be. These issues are not unimportant, as the earlier comments of the European Communities on the absence of a threshold have demonstrated. Given the much lower levels of endogenous production of these hormones by prepubertal children, the European Communities considers that the reply by Dr. De Brabander rightly points out the increased risk which repetitive exposure to such higher residues can present to the most sensitive parts of the population.

Q32. Please comment on the conclusions of the EC risk assessment (Opinion of the SCVPH of April 2002) that ultra sensitive methods to detect residues of hormones in animal tissues have become available but need further validation. What is the significance of this with regard to identifying whether the natural hormones in meat are endogenously produced or are residues of hormones used for growth promotion purposes?

EC Comments

The reply by Dr. Boisseau is scientifically unsound. As is very well explained by Dr. De Brabander's statement, there is an urgent need to apply the latest analytical methods to determine the nature and level of the residues from these hormones and all their metabolites, in view of the widespread use of meat and meat products. Moreover, precisely because of the endogenous production of the three natural hormones, it is imperative that the analytical method used should be able to determine accurately the true origin of residues in meat and their magnitude (i.e. endogenous or exogenous source).

Q33. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

EC Comments

The European Communities notes the conflicting replies of Dr. Boisseau and Dr. Boobis on the reasons for which JECFA decided to evaluate the three natural hormones in 1999 and on the significance of the establishment of ADIs for the first time.

The European Communities notes also the reply of Dr. Boisseau that the data on residues used in 1999 where the same as those used in 1988, in other words dated from the 1970s. As Dr. De Brabander correctly explains, these data should no longer be considered to be credible and reliable. It is therefore imperative that JECFA discloses to this Panel and the public the residues data it used in 1999 in order to verify in an open and objective manner the credibility and validity of its conclusion on the existence of a threshold, the lack of genotoxicity, etc.

Dr. Boobis admits that the 1988 evaluation was made by JECFA even without toxicological monographs, which means, *inter alia*, that for the two synthetic hormones – trenbolone acetate and zeranol – which have not been evaluated since 1988, JECFA's conclusions are no longer reliable. Moreover, Dr. Boobis accepts that: "…in the intervening time from the first to the second evaluation, it became clear that exposure to the natural hormones, albeit at levels appreciable higher that found in meat from treated cattle, could have adverse effects in humans. Hence, the implicit conclusion was that it was necessary to establish ADIs, to serve as health based guidance values. These could then be used as a benchmark for comparison with exposure via the diet." It is therefore remarkable that in the end JECFA did not recommend MRLs.

Q34. Please comment on the EC argument that the 1999 JECFA report based its findings on (a) outdated residues data and (b) not on evidence from residues in meat but on studies with experimental animals and on general studies of IARC. If the data were not new, did JECFA take this into account in its evaluation? What are the implications of using such data for the

purpose of conducting a risk assessment? How reliable are extrapolations from animal studies to possible adverse effects on humans? How does this compare with the kind of data and studies used with respect to other veterinary drugs? [see para. 120 of EC Rebuttal Submission (US case), para. 102 of EC Rebuttal (Canada case)]

EC Comments

The European Communities notes that both Dr. Boisseau and Dr. De Brabander agree in that the data used by JECFA in 1999 are old (since well before 1987). Dr. Boisseau usefully clarifies that some of them have even not been published in peer-reviewed scientific journals, as has been consistently arguing the European Communities in these proceedings. However, the argument advanced by Dr. Boisseau to minimise the importance of their old nature is not scientifically sound. For example, Dr. Boisseau does not explain how would it be possible to integrate in the risk assessment procedure conducted by JECFA in 1999 the residues of estradiol-esters and estradiol-alpha given that their specific hormonal or metabolic characteristics were not examined at all in the 1988 data? Moreover, concerning estradiol-alpha, which is the main metabolite found in target tissue (liver) of treated cattle and which we know that it will be metabolised in catechol derivatives, no specific evaluation of this genotoxic mechanism of action has been performed by JECFA. Against this background, is it possible for Dr. Boisseau that the quality of the data used by JECFA in 1999 was scientifically credible?

As has been explained above, on the critical questions of genotoxicity and the existence of a threshold, the level of endogenous production of the natural hormones by pre-pubertal children, etc., JECFA's evaluation hinged on a number of instances "on the balance" of the evidence (e.g. on the genotoxicity of oestradiol, progesterone, zeranol, etc.). Can Dr. Boisseau provide an assurance to the European Communities that JECFA's conclusions would have not been different if more recent and accurate data were available to it?

Q35. Please comment on the European Communities claim that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. Is this correct? Have subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies? [see para. 171 of EC Rebuttal Submission (US case), para. 161 of EC Rebuttal Submission (Canada case), para. 55, including footnote 60 of US First Submission and Exhibits CDA-20, 33, 34, and 35]

EC Comments

The European Communities notes that both Dr. Boisseau and Dr. De Brabander agree in that the data used in 2000 by JECFA for MGA date from the 1960s and 1970s. The explanation offered by Dr. Boisseau is not valid for basic the same reasons as those stated in its comment to the previous question. For instance, the "low-dose" issue was not recognised in peer-reviewed literature before the mid 90s. Thus, all the research into possible low-dose effects has not been considered in the 2000 JECFA report. In the light of the new evidence provided by the European Communities in its risk assessment of 1999, 2000 and 2002, showing so many gaps and uncertainties in our knowledge on MGA, can Dr. Boisseau assure the Panel that all the relevant and necessary scientific aspects about the safety of MGA have been completely and properly analysed and assessed or is it rather fair to say that there is a need for further research because of scientific uncertainties?

(c) Dose-response relationship

Q36. How would you describe a dose-response assessment? Is it, as suggested by Canada in para. 78 of its Rebuttal Submission, "widely, if not universally, accepted that adverse effects arising from hormonal activities are dose-dependent"? Is dose-response assessment a necessary component of hazard characterization? Or, is there an alternative approach which can replace

the dose-response assessment. Is a dose-response assessment feasible/necessary for substances that are found to be genotoxic or to have genotoxic potential? [see para. 153 of EC Replies to Panel Questions, para. 200 of EC Rebuttal Submission (US case); paras. 143, 154, and 156 of US First Submission, paras. 70-74 of US Replies to Panel Questions, and paras. 34 and 37-40 of US Rebuttal Submission; paras. 76-82 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with Dr. Cogliano's statement that "dose-response assessment is not a necessary component of hazard characterization." This is also consistent with the Appellate Body's 1998 decision in the *Hormones* case that a qualitative assessment of the risk is acceptable under the SPS Agreement. The European Communities also notes that Dr. Boobis accepts that "in Europe and generally within JECFA, once a compound is identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action, no exposure is considered without risk…". The European Communities also notes that the approach for such compounds that are known or assumed to exhibit no threshold in their dose-response curve, varies from one region to another, and this possibly explains the sharp difference between the parties to this dispute. What is also important to note is that there exist no internationally agreed guidelines on this issue, in the sense of Article 5.1 of the *SPS Agreement*. In the light of Dr. Boobis reply, the fact that the US and Canada have been arguing, on the basis of experience derived from their domestic practice, that the European Communities did not perform a dose-response assessment in this case is not really relevant.

Q37. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

EC Comments

The European Communities notes that Canada's argument that "…a dose-response assessment should *always* be conducted for chemical agents…" is not a scientifically sound nor a legally binding proposition. Both Dr. Boisseau and Dr. Boobis appear to agree with the EC argument contesting Canada's proposition. Furthermore, Dr. Boobis states that JECFA may consider a dose-response unnecessary for genotoxic substances, although this – in his view- "is a very unlikely occurrence for a veterinary drug because, in general, producers tend to screen out genotoxic compounds during the development process." However, Dr. Boobis does not probably take into account the fact that the hormones at issue have been approved in the US and Canada in the 1970s and since then the pharmaceutical industry did not carry out any kind of screening and did not generate new set of genotoxicity data.

(d) Sensitive populations

Q38. Please describe the range of physiological (or background) levels of the sex hormones in humans and identify the variations in these levels on the basis of age, sex group, and physiological stages.

EC Comments

The European Communities notes that Dr. Boisseau does not appear to contest the values stated in the SCVPH but rather whether the assays have been properly validated. However, it is not very uncommon in JECFA to use data from assays which are not yet properly validated. The European

Communities believes that the values from JECFA for serum 17β-oestradiol levels in prepubertal children are not correct. JECFA originally used the limit-of-detection as the "real" level when they could not measure the levels (or find it in the old literature as explained earlier). JECFA apparently questions the very low values determined by Klein et al., 1994, and Dr. Boobis suggest using "newer data from Klein (Klein et al., 1998)". However, Klein et al., 1998 only reports values for girls with precocious puberty, while they in the paper still refers to the original data (Klein et al., 1994) for the levels in normal prepubertal girls.

Dr. Boobis also writes that the values from another ultra sensitive bioassay (Paris et al., 2002) suggest that the levels are significantly higher, however, that assay measures estradiol equivalents (includes other natural estrogens and anything that may interact with the estrogen receptor). Nevertheless, even if the values from Paris et al., 2002 are used, they are still less than 1/3 the values shown in the table. Dr. Boisseau and Dr. Boobis ask if the bioassays have been properly validated. However, JECFA used the limit-of-detection when it could not measure the real values, which is clearly not acceptable! The real values for serum 17β-oestradiol in prepubertal children still remain to be properly documented. Since it is not possible to make the calculation on daily production rates without knowing the serum levels and the metabolic clearance rate in the most sensitive segment (children), and JECFA considers such data essential for determining an ADI, it must be accepted that JECFA cannot set the ADI and MRL before the values are known!

Q39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol-17β and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the populations which have been identified as particularly sensitive such as prepubertal children" [see para. 147 of the EC Replies to Panel Questions]

EC Comments

The European Communities notes that the replies of Dr. Boisseau conflict with those of Dr. Sippel. The European Communities agrees with Dr. Sippel's assessment, who demonstrates why there are a number of sources confirming the values mentioned by Klein et al, 1994 and 1999. Dr. Boisseau's reply is also false, because the SCVPH has performed – unlike JECFA which based its assessment on data from 1974 - the quantitative assessment taking account the lower endogenous production levels for pre-pubertal children from the most recent and reliable data (see also comments on previous question).

Q40. The European Communities states that "the levels of endogenous production of the hormones by prepubertal children is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship..." Please comment on the methodology used by the SCVPH to support the conclusion that hormone levels are lower than previously thought, and in particular comment on the validity of these methodologies and their conclusions. Would your conclusions have been the same at the time of adoption of the Directive in September 2003?

EC Comments

JECFA originally used the limit-of-detection as the "real" level when they could not measure the levels. Dr. Boobis suggest using "newer data from Klein (Klein et al., 1998)". However, Klein et al., 1998 only reports values for girls with precocious puberty, while they in the paper still refers to the original data (Klein et al., 1994) for the levels in normal pre-pubertal girls. Dr. Boobis also writes that the values from another ultra sensitive bioassay (Paris et al., 2002) suggest that the levels are significantly higher, however, that assay measures estradiol equivalents (includes other natural

estrogens and anything that may interact with the estrogen receptor). Nevertheless, even if the values from Paris et al., 2002 are used, they are still less than 1/3 of the JECFA values shown in the table. The real values for serum 17b-oestradiol in prepubertal children still remain to be properly documented, although Dr. Sippel provides convincing explanations and arguments to accept as valid the results from the RCBA assay.

Q41. Why would individuals with the lowest endogenous hormone levels be at greatest risk? How would the risks for these individuals arising from hormones naturally present in meat differ from the risks arising from the residues of hormone growth promoters?

EC Comments

The European Communities considers that the replies of the experts confirm the basic concerns in the 1999 SCVPH risk assessment about the need to protect the pre-pubertal children, and Dr. Sippel has summarised correctly the reasons. The replies by Dr. Boisseau and Dr. Boobis as to whether the risk would be the same or different are not entirely convincing. For instance, concerning estradiol-17-esters and estradiol-alpha found as residues in treated steers (Maume et al, APMIS 109 (2001) 32-38, Maume et al, Anal Chim Acta, 483 (2003) 289-297), it would not be true that the risks are the same. It is preferable to establish a rigorous risk assessment evaluation by considering specific classes of residues. The European Communities considers that the most important studies available provide a bioavailability rate which is 10% or higher (see the 2nd EC Written Submission).

Q42. To what extent, in your view, has JECFA taken into account the particular situation of sensitive populations, in particular prepubertal children, in its risk assessments with respect to oestradiol-17β? Please compare the original data concerning endogenous production of natural hormones by prepubertal children upon which JECFA based its assessment and those used by the European Communities in its risk assessment. In your view, does the scientific material referred to by the European Communities require a revision of the Codex recommendation with respect to oestradiol-17β? [For the questions in this section, see paras. 121-122 of EC Rebuttal Submission (US case), paras. 103-104 of EC Rebuttal Submission (Canada case), Exhibits EC-88, 99, para. 42-45 of US Rebuttal Submission, paras. 84 and 159 of US First Submission, and for JECFA's work Exhibits CDA-11, 16, 17, 18, 39]

EC Comments

The European Communities notes the replies of Dr. Boisseau and Dr. Boobis, who incidentally have not carried out any research themselves on these hormones and so have no specific expertise, are very monolithic and one-sided. Their views are based again on the assumptions that this hormone is not genotoxic and that the rate of endogenous production by prepubertal children is correctly cited in the JECFA report. But if an over-estimation of endogenous levels and production rates would exist, as the more recent evidence demonstrates, then a revision would be immediately necessary. And there are so many other reasons to believe that the JECFA evaluation is scientifically wrong, as explained above (old and unreliable data, etc.), no reliance can be placed on the replies by these two experts.

(e) Bioavailability

Q43. Please define bioavailability, comment on the significance of bioavailability to assessments of risk, and on the degree of bioavailability of the residues of the hormones at issue when consumed in meat, taking into account parties' differing views on this matter. [see paras. 123-124 of EC Rebuttal Submission (US case), para. 105-106 of EC Rebuttal Submission (Canada case), paras. 100, 155-159 of the EC Replies to Panel Questions, paras. 32 and 41-42 of US Rebuttal Submission, paras. 69, 71, 88-89 and 146 of US First Submission, and para. 134 of Canada Rebuttal Submission]

EC Comments

The European Communities agrees with the summary on this question as stated by Dr. Guttenplan. Indeed, Dr. Boisseau writes "oestradiol-17β is inactive orally". This is simply factually wrong! Oestradiol-17β is routinely administrated to humans as a powder or in the form of pills that are taken orally. For example, in the study reported by Lampit et al., 2002, the girls were administrated 8 µg conjugated oestradiol-17β in the form of encapsulated powder. Moreover, in the "benchmark study" on oestradiol-17β performed in rats (Cook et al., 1998) the rats were orally dosed with oestradiol-17β. Thus, there are no doubts that oestradiol-17β is orally active.[9] It is also not disputed that no rigorous procedure has been used to assess hormonal risk concerning estradiol-ester, in particular on absorption via the lymphatic route. It is clear that estradiol and estradiol-esters are not devoid of effect when given orally (Paris et al, APMIS, 2001).

The European Communities has provided credible recent evidence that the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account). Moreover, the calculations presented in the SCVPH assessment clearly that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children. As Dr. Guttenplan states, this would represent a risk factor. Neither Dr. Boisseau nor Dr. Boobis provide a specific reply to this other than repeating the general and hypothetical assumptions of JECFA that their bioavailability "is rather low". It should also be noted that the bioavailability of the three synthetic hormones has not been determined by JECFA.

(f) Good veterinary practice (GVP)

Q44. Please define "good veterinary practice" (GVP) and/or "good practice in the use of veterinary drugs" (GPVD). What are the relevant Codex standards, guidelines or recommendations relating to GVP/GPVD? Please comment on the statement by the European Communities that the definition of the GPVD is "circular and hence problematic." [see para. 88 of the EC Replies to Panel Questions]

EC Comments

The statement by Dr. Boisseau that "Codex did not adopt any guideline on GVP aimed at minimizing the occurrence of veterinary drug residues in animal derived food" confirms what the European Communities has always been arguing. The European Communities recalls that the Appellate Body in the 1998 *Hormones* decision has held that:

> "… We consider that the object and purpose of the SPS Agreement justify the examination and evaluation of all such risks for human health whatever their precise and immediate origin may be. We do not mean to suggest that risks arising from potential abuse in the administration of controlled substances and from control problems need to be, or should be, evaluated by risk assessors in each and every case. When and if risks of these types do in fact arise, risk assessors may examine and evaluate them. Clearly, the necessity or propriety of examination and evaluation of such risks would have to be addressed on a case-by-case basis. What, in our view, is a fundamental legal error is to exclude, on an a priori basis, any such risks from the scope of application of Articles 5.1 and 5.2 …". (at para. 206)

[9] See Cook J.C., Johnson L., O'Connor J.C., Biegel L.B., Krams C.H., Frame S.R., Hurtt M.E.: Effects of dietary 17 beta-estradiol exposure on serum hormone concentrations and testicular parameters in male Crl:CD BR rats, Toxicol Sci. 1998 44:155-68.

The European Communities also recalls that the inspections and measurements of hormone residues in US meat made by the European Communities revealed that hormones were found in what was supposed to be a "guaranteed hormone-free beef", and that the levels of one of the hormones (MGA) were too high to be achieved by the legal dosing. The European Communities has also performed two specific risk assessments for the US and Canada that comply with the requirements laid down in para. 206 of the Appellate Body report mentioned above (see in particular EC exhibits 67-73). Thus, there is specific evidence proving that GVP is not followed by at least by some meat producers in the US and Canada. The debate on this issue demonstrates, as Dr. De Brabander shows, that there is an important difference between the theoretical assumption of respecting GVP and real life.

Q45. In conducting a risk assessment of specific veterinary drugs, what assumptions are made concerning GVP, if any? How, if at all, are risks that might arise from the failure to follow good veterinary practice in the administration of veterinary drugs addressed?

EC Comments

As Dr. Boisseau states, the Codex recommendations (whether ADIs or MRLs) "are only meaningful in countries where GVP are effectively implemented." There is, however, plenty and undisputed evidence that frequently GVP is not respected in the US and Canada (although Canada appears to have a slightly better record). However, as Dr. De Brabander rightly explains, the argument of Dr. Boisseau is not correct that risk assessors cannot take into account possible misuse or abuse in their assessment, as the 1999 and 2002 SCVPH opinions have clearly demonstrated and as Dr. Boobis also admits in his reply to question no 46.

Q46. To what extent were risks from misuse or abuse assessed by JECFA in its evaluation of the hormones at issue? In terms of the three synthetic hormones at issue, how is GVP relevant to the establishment of MRLs by JECFA?

EC Comments

Although the theoretical description by Dr. Boobis is more or less accurate, the important point is that the pharmaceutical industry did not carry out any systematic experiments on possible misuse or abuse of these hormones nor did it submit such data to the US and Canadian regulatory authorities in the 1970 and 1980s when applied for the authorisation of these substances. The result is that also JECFA, which based its evaluation on the same old data, did not consider systematically the issue of possible misuse or abuse. This is a fundamental flaw in JECFA's assessment of these hormones.

As the European Communities has already explained, even the US authorities now accept (see e.g. the 2002 US Carcinogenesis Report) that the administration of these hormones to cattle, which presumably respects GVP, leads to residue levels that exceed the levels from endogenous production. This means that when misuse or abuse occurs the excess levels are inevitably going to be much higher. According to the studies cited by the European Communities, e.g. Exhibits EC-12 and 17 and 73, the level of residues in case of misuse or abuse by far exceed the ADIs recommended by JECFA and the acceptable levels and tolerances recommended in the US and Canada.

Q47. How significant are any differences in GVP in the European Communities, the United States, and Canada? Does the EC risk assessment take into account relevant control mechanisms with respect to GVP in place in the United States and/or Canada? If so, what are their conclusions?

EC Comments

The statement of Dr. Boisseau is partly false. The European Communities has carried out a specific assessment of the US and Canadian situation concerning respect of GVP (see EC Exhibits 67 and 68) and has taken into account the multiple sources of misuse and abuse that frequently occur there (see EC Exhibits 69 -70, and 71-72, 96, and 102-103). As Dr. Boisseau states these hormones are sold over the counter in the US and Canada, which means that there is in reality no way to control their possible misuse by the authorities there. The evidence available does show that such misuse or abuse occurs frequently, because these hormones are administered in combinations and the farmers have incentives to apply multiple doses.

Q48. To what extent does the scientific evidence referred to by the European Communities assess risks to human health from residues of misplaced implants or improper administration, i.e. when administered differently than indicated on the label of the manufacturer or contrary to GVP, of any of the six hormones? Would your reply have been different at the time of adoption of the EC Directive in September 2003? What are the potential hazards, if any, to human health of the use of large quantities, or doses higher than recommended, of any of the six hormones in dispute?

EC Comments

The criticism of both Dr. Boisseau and Dr. Boobis is based on their understanding that the European Communities did not perform a quantitative risk assessment, which they think is a necessary requirement for a proper risk assessment under the SPS. However, as the European Communities has explained several times in previous questions, this in not required under the *SPS Agreement* as interpreted by the Appellate Body. But as already explained, the European Communities has nevertheless performed a quantitative dose-response assessment in particular with regard to prepubertal children. As the exposure from residues in meat *treated with these hormones according to GVP* was found to lead to residues that exceeded several times the ADIs and MRLs, it is obvious that the higher levels of residues that will inevitably result from misuse or abuse of these hormones will also exceed the ADIs and MRLs recommended by JECFA.

Furthermore, Dr. Boobis states that "…the potential risk, i.e. the probability that effects would occur, would depend on a number of factors...". But as the European Communities has already explained, the risk and risk assessment under the *SPS Agreement*, as interpreted by the Appellate Body, is not the "probability" of the identified risk occurring but the "possibility" of the identified risk occurring under real conditions of use.

Q49. What analytical methods, or other technical means, for residue detection in tissues exist to control the use of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice? What tools are available to control the use by farmers of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice?

EC Comments

To the list of tools listed by Dr. De Brabander to control the possible misuse or abuse of these hormones, the European Communities would add that these hormones should not be sold freely on the counter but by veterinary prescription only. Of course all these apply only for the countries that would be prepared to assume that the possible risk would not undermine their chosen level of health protection.

Q50. Are there other measures available to the European Communities (other than a complete ban) which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

EC Comments

The European Communities notes that the replies by Dr. Boisseau and Dr. De Brabander agree on the point that if GVP is not respected, then the importing country should have the right to restrict imports, even with a total ban, depending on the importing country's chosen level of health protection.

Q51. Does the material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada call into question the potential applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada?

EC Comments

The European Communities understands that the answer by Dr. Boisseau to this question is that the Codex standards would not be applicable. The European Communities also agrees with the statement by Dr. De Brabander.

(g) Other

Q52. Do the risk assessment of the European Communities or any other scientific materials referred to by the European Communities demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes? If yes, why? If not, what kind of evidence would be required to demonstrate such potential adverse affects? Would your response have been different at the time of adoption of the Directive in September 2003?

EC Comments

The European Communities considers that the statements by Dr. Boisseau and Dr. Boobis are scientifically incorrect because they are based on many assumptions and conservative interpretation of the available and constantly growing evidence that directly implicates these hormones in causing and promoting cancer and a number of other adverse effects in humans. If the views of these experts were to be adopted the prerogative of cautious public authorities to regulate risk in order to reduce or eliminate it would completely vanish. Dr. Boisseau and Dr. Boobis apply double standards because they require for the prohibition of these hormones evidence which the pharmaceutical industry did not provide nor did it even examine when it applied for the approval of these substances in the US and Canada in the 1970s and 1980s.

Dr. Boisseau states that: "… the kind of evidence required to demonstrate such potential adverse effects should be (1) toxicological data indicating that the values of the ADIs established by JECFA are not conservative enough, (2) data on residues in treated/non treated cattle and on daily production of hormones in sensitive individuals indicating that the hormonal residue intake associated with the consumption of meat from treated cattle is such that the established ADIs would be exceeded in the case of use of growth promoters." The European Communities submits that such data have been provided and taken into account in the 1999, 2000 and 2002 SCVPH risk assessment, which he has apparently not properly examined.

Dr. Boobis states again that: "… the weight of evidence is that the hormones are not genotoxic in vivo even at doses well above those that would be present in meat from treated cattle (…) However, all of the major reviews in this topic have concluded that whilst there are data gaps, there is no evidence that low level exposure is causing harmful effects in humans (…) However, it should be emphasised that on the basis of the information available, I would rate the risk of adverse effects in humans consuming meat from treated cattle as minimal." (emphasis added). So, according to Dr. Boobis conservative reading of "the weight of available evidence", which means that scientific views outside the mainstream or the majority held view do not count for him, it cannot be excluded that there is a risk, even though this is evaluated by him to be "minimal". However, he does not explain what is "minimal" risk, nor does he seem to pay any attention to the fact that the "gaps in our knowledge – which he admits exist – may indicate that there is scientific uncertainty with potentially disastrous consequences for the consumers.

The European Communities considers that Dr. Guttenplan has rightly summarised the issue: the evidence which the European Communities has presented suggests that "even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen exceeding the daily production rate of oestradiol in prepubertal children". When the evidence is not to their liking, the US and Canada contest the accuracy of the assay originally employed for estrogens at the low levels found in children. However, they consistently refuse, as dose JECFA, to provide their old data in order to examine in an open and transparent manner the kind of assays used by the pharmaceutical industry in the 1970s and 1980s for the approval of these hormones in the US and Canada. But as Dr. Guttenplan rightly points out, recent reports indicate that "more recently reported levels used by the EC are accurate. In addition, levels in post-menopausal women were also very low." Moreover, he explains that: "For pre-pubertal children, even with the low bioavailability of estrogen along with and its low levels in meats, it appears possible that intake levels would be within an order of magnitude of those of the daily production rate. This is greater than FDA's ADI and suggests some risk to this population."

Q53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations? Would the systematic use of these and the synthetic hormones in combination have any implications on how the scientific experiments and the risk assessments are to be carried out? If so, have the scientific materials referred to by the European Communities or relevant JECFA reports taken into account the possible synergistic effects of such combinations on human health? [see sections 4.2-4.3 of the Opinion of the SCVPH of 2002 in US Exhibit 1]

EC Comments

The European Communities notes that both Dr. Boisseau and Dr. Guttenplan recognise that the statement by the European Communities is correct. Dr. Boisseau's reply is, however, partly false because it ignores the potential stimulatory estrogen receptor mediated effects of estradiol on cell proliferation which tend to be increased by progestins (see *New Eng. J. Med., 354, 270-282, 2006)*.

Moreover, Dr. Guttenplan accepts that "… in principle the use of mixtures should complicate risk assessments/scientific experiments, as they would have to evaluate/investigate each component alone and in combination. This is a major undertaking as effects of individual agents may be additive, inhibitory, and synergistic or there may no effect." What is even more important, he acknowledges that "… it appears that no experiments on effects of combinations were performed, so some uncertainty exists there." The European Communities submits that this is still another kind of uncertainty that should be taken into account by the Panel in deciding whether the evaluations by JECFA are credible and reliable.

Q54. What is the acceptable level of risk reflected in the Codex standards for the five hormones at issue? How does this compare to the European Communities' stated objective of "no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion". [see para. 149 of EC Rebuttal Submission (US case)]

EC Comments

The European Communities notes that Dr. Boisseau and Dr. Boobis differ as to the acceptable level of risk reflected in the Codex standards for the five hormones at issue: the first argues that Codex's "... ADI represents the quantity of these residues which can be ingested daily by consumers over life time *without causing any problem* of health ...", but the reply of the second suggests that the level is "*no appreciable risk with daily exposure*". If one were to follow Dr. Boisseau's reply, then there is no doubt, and most of the experts have explicitly accepted it, that there is a risk although for some of them – like Dr. Boobis - this is viewed as "minimal". On the other hand, if Dr. Boobis' reply is followed, this would mean that Codex's standard recognises that there is an scientifically identified risk but recommends its members to follow it because it thinks (as a risk manager) that it is "not appreciable". If that were the case, however, Codex and the *SPS Agreement* cannot oblige a sovereign country to accept a risk, whether it is viewed as small, medium or big. This is the autonomous right of each member to decide and the Appellate Body has explicitly said that WTO members have the right to fix a level of protection of "zero risk".

For the benefit of Dr. Guttenplan, Codex has not set an ADI or an MRL for MGA yet, since no decision has been taken by the Codex Alimentarius Commission. So, no international standard exists for MGA yet.

Q55. Do the Opinions of the European Communities or other scientific materials referred to by the European Communities evaluate the extent to which residues of growth promoting hormones in meat contribute to what the European Communities calls "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings"? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 151 of EC Replies to Panel Questions, paras. 43-44 of US Rebuttal Submission, paras. 83-85 of Canada's Rebuttal Submission]

EC Comments

The European Communities disagrees with Dr. Boisseau's reply that its position is "a position of principle" or that it is based on economic grounds (as he implied with his reply to the previous question). The time, effort and money spent by the European Communities to clarify the scientific issues identified by the Appellate Body in its 1998 report on *Hormones* clearly establish that the EC's position and legislation are based on sound and up to date scientific grounds. The precautionary principle comes after proper consideration of the scientifically identified and analysed risk.

Dr. Boobis accepts that additive risks arising from the cumulative exposures is a scientifically sound approach and that can and is done in some cases. From his reply, one may infer that he accepts that this is not done by JECFA nor by the US and Canada. He only thinks this is not appropriate for these hormones because of his preconceived approach that there is a dose-response relationship (threshold) in the carcinogenic mode of action of these hormones.

The European Communities disagrees with the statements by Dr. Boisseau and Dr. Boobis for the reasons that have been developed extensively in its submissions and in some of its comments above. It urges the Panel to disregard their comments because they are purely theoretical and for the additional reason that they come from two experts that have never done any specific research on these hormones

nor have they ever published something on these substances. Instead of criticising the risk assessment produced by the European Communities, these experts should have examined in their replies whether such an additive risk assessment ought to have been examined by JECFA in the first place before issuing the recommendation that the risk is "not significant".

The European Communities notes that Dr. Guttenplan would have liked to see much more evidence in the 1999 SCVPH assessment. To the extent this was not provided in 1999 and in 2002, this is not because of omission but because the state of scientific knowledge available by then – i.e. the gaps and scientific uncertainty clearly identified in those opinions – did not allow such an assessment to be completed.

Q56. Has JECFA/Codex considered in its risk assessment of the five hormones such "additive risks? Are there internationally recognized guidelines for conducting assessments of "additive risks"?

EC Comments

The European Communities disagrees with both Dr. Boisseau's and Dr. Boobis' replies. They provide no precise reference of where in the JECFA 2000 report it is stated that such a cumulative risk assessment was carried out. The European Communities understands that such a cumulative assessment of the additive risk has not been performed (and this is also what apparently Dr. Guttenplan believes, as words seem to be missing from his reply).

The European Communities notes that it has clearly been shown that the effects from exposure to different estrogens are additive; i.e. when several estrogens are given simultaneously at concentrations where none of them alone results in any detectable effects, the combined exposure leads to a clear effect. Thus, any additional dose will lead to an increased effect (Rajapakse N., Silva E., Kortenkamp A.: Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action., Envir. Health Perspec. 110, 917-921 (2002); and Tinwell H., Ashby J.: Sensitivity of the Immature Rat Uterotrophic Assay to Mixtures of Estrogens, Envir. Health Perspec.112, 575-582 (2004)). Moreover, there are several hormonal preparations containing two hormones (estradiol plus trenbolone) and there are several publications in the animal science literature recommending different preparations in consecutive applications. Therefore, the additive risk needs to be carefully evaluated. For instance, trenbolone as such has a complex hormonal activity (at the same time progestin, androgen and glucocorticoid). Estradiol and trenbolone residues therefore may have 4 different hormonal activities.

The European Communities further notes that although there is agreement that "there is no international agreement on how to undertake a combined risk assessment of compounds acting by the carcinogenic mechanisms suggested by the EC for the hormones, i.e. genotoxicity via direct or indirect interaction with DNA", yet the performance of such a risk assessment is not impossible. The European Communities has tried to do such an assessment when the information available was sufficient, but could not complete it because of gaps in our scientific knowledge.

Q57. Canada comments that "one single molecule that the European Communities considers so dangerous from meat derived from animals treated with hormone growth promoters is suddenly not at all that dangerous when consumed from meat from animals treated for therapeutic or zootechnical purposes. The European Communities' concern about the genotoxic potential of oestradiol-17β suddenly and inexplicably disappears." To what extent are hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes, taken into account by the European Communities, if at all, in its assessment of the cumulative effects from the consumption of meat containing residues of the hormones at issue? Would your reply have been different at the time of adoption of the EC

Directive in September 2003? If so, why? [see para. 97 of Canada Rebuttal Submission; paras. 17-20 of US Opening Statement]

EC Comments

The European Communities considers that asking this question in the first place was unnecessary and irrelevant, because the Appellate Body did not find any violation from the use of some of these hormones for therapeutical or zootechnical purposes. As Dr. Guttenplan points out, the conditions imposed by the European Communities for such limited use are such that it would not be possible to undermine its chosen level of protection.

Therefore, the European Communities is consistent because the use of oestradiol for such purposes is now virtually terminated.

Q58. Please comment on the EC statement in para. 94 of the EC Replies to Panel Questions that "the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be", taking into account para. 105 of Canada Rebuttal Submission.

EC Comments

The European Communities needs to clarify that the quoted statement was made in response to the US and indeed Canadian argument that there is no risk from cumulative exposure to residue of these hormones in meat treated with one or several of these hormones for growth promotion purposes. Moreover, the statement is framed cautiously to say "is likely to be" precisely because such a complete cumulative risk assessment has not been carried out by JECFA and the other countries. Moreover, if the assumption of JECFA and of the US and Canada that there is a threshold is false, the relevance of the EC comment is a realistic eventuality. The European Communities has in fact provided the Panel with recent evidence (e.g. the papers by Dr. D. Sheehan, see Exhibit EC-87) which has showed the absence of such a threshold. It is indicative that none of the experts discuss it in his replies. The studies mentioned in these exhibits show that under the circumstance that the endogenous hormone is active, there can be no threshold unless metabolism is 100% effective before the dose reaches the target tissue. It is also noteworthy that none of the scientists discusses the reference made by the European Communities to the US 2002 Carcinogenesis Report which states as regards oestradiol that residues in meat from animals treated with hormones for growth promotion lead to levels higher than the endogenously produced ones. The question therefore is by how much and of what kind of biological and toxicological nature. In the EC's comments to previous questions, it has been shown that the level of residue formation in meat can be significantly higher and may contain residues from different metabolites. It seems therefore that the experts criticise the European Communities for making an assumption, but they are not apparently able to prove either that their own assumption is correct.

Q59. Does the scientific evidence referred to by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see para. 132 of Canada Rebuttal Submission]

EC Comments

The European Communities notes the different views which the replies of the scientists display on this critical question. Dr. Boisseau accepts that such adverse effects have been identified, but faults the European Communities for not having conducted a "quantitative" risk assessment. Dr. Boobis

continues with his line of argument that there is a threshold effect, which prevents this kind of adverse effects on the immune system from occurring. The point, however, is that neither the US nor Canada (and a fortiori nor JECFA) have identified such adverse effects because of the outdated nature of the data on which they based their assessments. The European Communities has offered some serious evidence, some of which appeared for the first time recently, and pointed to a number of gaps and uncertainty in our knowledge. This is recognised by Dr. Guttenplan, who states that "…there is evidence that estrogens can be involved in Lupus, rheumatoid arthritis, thyroiditis. In addition the development of allergies is thought to be at least partially related to estrogens. The studies in experimental animals also did not identify any immune-related effects, although it is not certain the types of possible effects in humans would be detected in experimental animals…". The question, therefore, is the degree of confidence by which the US and Canada (and JECFA) can ensure the Panel that such adverse immune effects are not possible to occur from residues in meat treated with these hormones for animal growth promotion. The European Communities thinks they have failed to do so to the required standard of proof.

Q60. Does the scientific evidence referred to by the European Communities identify and evaluate whether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives (MGA) or implanted? Are you aware of any differences?

EC Comments

The EC contests the accuracy of the statements by Dr. Boisseau and Dr. Boobis. It is known that MGA is the only hormone that is administered as a feed additive, which confirms that the bioavailability of this hormone is rather high. Moreover, it has been shown that MGA is highly lipophilic and accumulates in adipose tissue. The 1999 and 2002 SCVPH and exhibits EC-14, 16 and 19 have shown that the route of administration of MGA is conducive to misuse or abuse, as the residues of MGA detected in the US samples of meet were much higher than the levels which should have been normally expected (exhibit EC-16). The study mentioned in exhibit EC-16 has also shown that the residues in fat of oestradiol-17β increased by about 300% following labelled MGA treatment. The consequence of this is that given the tremendous "boosting" effect which MGA has on the residues of oestradiol in meat and the easiness by which its administration can be misused, the possibility to increase substantially the level of residues, and hence the risk of cancer, is significantly increased. This is not examined either by Dr. Boisseau or Dr. Boobis, who apparently have not read this material.

Hormone MGA has been in use in the US and Canada since the 1970s and it is interesting to note that JECFA has not been seized of a request to evaluate it until 2000. Yet, until today there is no Codex standard for MGA. It is also clear that the evidence upon which JECFA based its evaluation has not been made available to anyone, has not been published in peer-reviewed journals and it is outdated but today's standards. The most important evidence on MGA is the one generated by the EC following the Appellate Body 1998 hormones decision. This information is publicly available and demonstrates the gaps in our knowledge, the uncertainty surrounding this hormone and the multiple risks which the administration of MGA poses to human health.

As regards the risks from eating meat treated with implanted hormones, the evidence shows that non-removed implants contain milligrams of residues. These are 10^7 to 10^9 fold more residues than present in the peripheral tissue (pikograms per gram). The total dosage in an implantation site is therefore about a thousand fold higher than the residues in the whole carcass of the animal. There is no doubt that the risk from implanted hormones is in a completely different order of magnitude from the risk posed from untreated animals. Dr. Boobis makes again his unfounded statement that: "However, whilst this would lead to increased exposures, it is still unlikely this would exceed the ADI, and

certainly not for any period of time. It is also an unlikely occurrence in view of the way in which the hormones are used and controlled." First of all, he has and provides no factual basis to argue that it is "unlikely" that misuse will exceed the ADI. Neither Codex nor JECFA have fixed yet an ADI, and even if they were to do it one day, he has now no data to suggest that it is unlikely to be exceeded. Moreover, it has already been shown that even the administration of MGA that does respects GVP leads to a tremendous "boosting" effect on the residues of oestradiol in fat and the attending risk of exceeding the ADIs is very high.

Q61. In your view and in the light of information provided by the parties as well as the work undertaken at JECFA and Codex, did the scientific evidence available to the European Communities at the time it adopted its Directive (September 2003) allow it to conduct an assessment (quantitatively or qualitatively) of the potential for adverse effects on human health arising from the consumption of meat from cattle treated with (a) progesterone; (b) testosterone; (c) trenbolone; (d) zeranol; and (e) melengestrol acetate? Would your response differ in light of the scientific evidence provided which is subsequent to the adoption of the EC Directive?

EC Comments

The reply of Dr. Boisseau is surprising as the data available to the EC are mentioned in the 1999, 2000 and 2002 SCVPH assessments and the additional evidence from other sources is explained in the written submissions of the EC to the Panel and were provided as exhibits thereto. It is recalled that he has explicitly admitted that he has not done nor published any work on these hormones.

The reply by Dr. Boobis and Dr. Boisseau can only be explained by their exclusive reliance on the JECFA reports, which Dr. Boobis thinks represent the "weight of the evidence" that should be taken into account. This is probably not surprising, as they have both served in the JECFA panel that examined some of these hormones, although they both lack any specific expertise on these hormones, as they have not carried themselves any experiment on them when used for animal growth promotion purposes.

Their entire reasoning – whose objectivity and impartiality is therefore in great doubt for the reasons the EC has explained to the Panel during the expert selection procedure - is based on the assumption that there is a dose-response relationship (threshold), despite the accumulation of so much recent evidence showing that this assumption can no longer be valid for a number of these hormones, certainly for oestradiol 17β, progesterone, testosterone and zeranol. Their reasoning is also based on the idea that a risk assessment to be acceptable has to perform a quantitative analysis and assessment of risk even of aspects for which the available evidence is insufficient or there are total areas of gaps in our knowledge.

The EC considers that the reply by Dr. Guttenplan, as well as those by Dr. Shippel, Dr. De Brabander and Dr. Cogliano who have not expressed themselves on this precise question but this can be seen from their replies to the other questions, show that there is sufficient evidence which "does indicate that potential adverse effects exist for all of the hormones. However, the ability to make a risk assessment (qualitative or qualitative) does vary between compounds." (Dr. Guttenplan). The available evidence, at the varying degrees mentioned by Dr. Guttenplan, does establish that "… accurate ADI's cannot be established at this point", and that "… studies in experimental animals and studies on levels in beef are still needed." Most importantly, the EC agrees that "from the data available at the time of the Directive, the potential for adverse effects could not be ruled out."

Q62. Does the scientific evidence relied upon by the European Communities support the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge

now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why?

EC Comments

The EC considers that its comments on the positions of Dr. Boisseau and Dr. Boobis to the previous question no. 61 are equally and fully applicable here.

It is difficult to grasp the idea of Dr. Boisseau for a temporary risk assessment, unless his statement was to be understood that the gaps and uncertainties identified by the EC in its risk assessment are such as to require further research and investigation.

As regards the long and dismissive reply by Dr. Boobis, who despite his lack of any specific expertise on these hormones tried to discredit all the studies mentioned by the EC, it is now clear on the basis of a more careful examination by a real expert of the same body of evidence that it would necessarily lead to the opposite conclusion. Dr. Boobis' comments on the studies generated by the EC are flawed in almost all respects.

For instance, he comments on the Leffers et al., 2001 study on the low-dose effects of Zeranol and other estrogens on gene expression in MCF7 cells. He writes: "Many of the changes will reflect the proliferative response to an oestrogenic stimulus". However, in the applied assay changes in gene expression were assayed after 24h exposure, whereas the first up-regulation of proliferation-sensitive genes becomes detectable after 36h exposure. Thus, the observed effects are a likely direct consequence of gene activation by the estrogen receptor, reflecting activation of the receptor by Zeranol and the other compounds. (see Jorgensen M., Hummel R., Bevort M., Andersson A.M., Skakkebaek N.E., Leffers H.: Detection of oestrogenic chemicals by assaying the expression level of oestrogen regulated genes. APMIS. 1998 106:245-51.)

Another example is that he dismisses the bovine metabolism of oestradiol-17β and oestrogenic potency of fatty acid residues on the unsubstantiated ground that "the difference in potency from the parent hormone is not very great or even apparent at low doses, where effects were minimal", where the opposite is rather true in the study cited. Another example is that he dismisses the relevance of the studies on misuse and abuse on the speculative ground that "… the probability that this would occur is extremely low". However, he has no evidence and provides no credible basis for that conclusion. Still another example is that he dismisses the relevance of the recent findings on the mutagenicity and genotoxicity of oestradiol-17β despite the fact that this has been shown both in vitro and now in vivo. The findings of the study he criticises for no valid reason have been largely confirmed in other recent studies supporting a role for the estrogen metabolites which include the genotoxic, mutagenic estrogen quinones in estrogen carcinogenicity (New Eng. J. Med., 354, 270-282, 2006). And the list of examples showing lack of specific knowledge or impartial presentation of the available evidence by Dr. Boobis is much longer.

Conversely, a more considered and objective view is to be found in the reply of Dr. Guttenplan, who provides some examples of the areas in which gaps and uncertainties have been identified and indicates some of the additional research that is required before the EC would be able to conduct a more complete risk assessment. The EC agrees with his comments.

ANNEX F-2

COMMENTS BY THE EUROPEAN COMMUNITIES ON THE REPLIES OF CODEX, JEFCA AND IARC ON QUESTIONS POSED BY THE PANEL

(30 June 2006)

Introduction

The European Communities appreciates this opportunity to comment on the replies of the international bodies to the questions posed to them by the Panel. The European Communities considers it necessary to recall the position it has already expressed to the Panel at the time it decided to ask questions from these bodies, namely that Codex and JECFA lack appropriate and transparent procedures for submitting this kind of comments and replies to other international organisations, such as the WTO dispute settlement bodies. In particular, replies and comments that come simply from the secretariat of those bodies, without following the legally required procedures for their internal elaboration and transmission, should be disregarded because they are likely to influence unlawfully the Panel's deliberations.

The European Communities notes that the comments submitted in these cases by those bodies do not explain whether the required internal rules and procedures for their adoption have been fully respected. Therefore, the European Communities requests the Panel to clarify this question with these bodies; in the absence of an adequate and legally sound reply – with precise references to the rules that were applied in the elaboration of their replies - the European Communities would request the Panel to disregard them.

Q1. Please briefly describe the procedure for the elaboration and adoption of an international standard by Codex. What is the decision-making process for the adoption of an international standard?

EC Comments

The European Communities notes that according to Codex: "In the case of MRLs for veterinary drugs, submission of project documents is not required; instead, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) prepares a priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA, which is submitted to the Commission for approval." However, it is noteworthy that this procedure was not followed when JECFA decided to re-evaluate the three natural hormones in 1999, because the CCRVDF did not request such a re-evaluation.

The European Communities also notes the statement whereby: "The Commission attaches a great importance of achieving consensus at all stages of the elaboration of standards and that draft standards should, as a matter of principle, be submitted to the Commission for adoption only where consensus has been achieved at the technical level." However, the European Communities draws the attention of the Panel to the uncontested fact that the 1988 Codex standards for the five hormones (except MGA) were not adopted by consensus and the 1999 review by JECFA of only the three natural hormones were not even presented to Codex for adoption because the relevant committee [CCRVDF] decided not to consider them as it had not requested their re-evaluation.

Q2. Please briefly explain the differences between Codex standards, codes of practice, guidelines, principles and other recommendations.

EC Comments

The EC has no comments at this stage.

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

EC Comments

As the European Communities explained by its comments to question no 3 of the Panel experts questions, its legislation complies with the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius,* which where adopted by Codex in 2003, and these working principles were complied with in the assessment of the six hormones at issue and in the adoption of the Hormones Directive 2003/74/EC.

The European Communities further notes the statement that: "Following the adoption of the Working Principles, the Commission requested that relevant Codex Committees develop or complete specific guidelines on risk analysis in their respective areas for inclusion in the Procedural Manual…The two documents will be considered by the 30th Session of the Codex Alimentarius Commission in 2007 (after review by the Codex Committee on General Principles) for adoption and inclusion in the Procedural Manual." This statement confirms the EC position (see also its comments to question no 3 of the Panel experts questions) that until now there exist no guidelines on risk analysis for residues of veterinary drugs in the sense of Article 5.1 of the *SPS Agreement*. The consideration in 2007 of the two working documents does not mean that they will be adopted, if one were to judge from previous experience in the work of the Codex Committee on General Principles.

The European Communities also draws the attention of the Panel to the statement that the principles to be adopted one day will "…define the responsibilities of the various parties involved: the responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods, while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA)." This confirms again the EC position (see also the EC comments to question no 5 of the Panel experts questions) that such a clear definition of the responsibilities does currently not exist, and that in reality it is JECFA that is informally doing also the risk management, leaving practically no real risk management choice to the Codex members to adopt measures aiming to achieve a high level of health protection. This is clearly the situation in the case of the six hormones in dispute, since the old data used by JECFA and the way in which it drafted its reports (e.g. "genotoxic potential", "unlikely to be exceeded", "pose an insignificant risk", "MRLs considered unnecessary", etc.) in effect deprive the Codex members from applying a very high level of protection, which in the context of the WTO can be "no or zero (additive) risk" according to the Appellate Body.

The European Communities considers that the reply of JECFA confirms the EC position that there exists currently no international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues in food. What JECFA calls "key international risk assessment documents" are in reality nothing more than informal papers prepared for certain specific purposes and substances which were never presented for consideration and adoption by the competent decision-making bodies of Codex Alimentarius Commission and JECFA. They do not have, therefore the status of legally binding risk assessment techniques in the sense of Article 5.1 of the *SPS Agreement*. In fact, if such risk assessment techniques already existed, quod non, there would have been no need to start this kind of work in the CCRVDF in 2000. Indeed, the reply of Codex to the next question (No 4) confirms explicitly the accuracy of the EC position.

It should be further clarified that the above EC comments do not intent to diminish the work that is being done in the framework of Codex and JECFA, which is of importance primarily for the countries which do not have in their internal legislation such rules and procedures on risk assessment. The informal technical work to which JECFA and Codex refer cannot, However, be invoked to resolve differences between the parties in a formal WTO dispute settlement with very serious legal, health and economic consequences for the parties to the dispute. This could be the case only when Codex and JECFA formally adopt some time in the future the relevant standards on risk assessment for this kind of residues of veterinary drugs in food. As the European Communities has explained with its comments on question no 3 of the Panel experts questions, its internal legislation on risk assessment applied to the six hormones in question is far more advanced than the informal working documents to which Codex and JECFA referred to in their replies.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

EC Comments

The European Communities notes the reply of Codex that: "There is no adopted Codex standard or related text on the risk assessment of residues on veterinary drugs that provides guidance to governments (…) the CCRVDF in 2000 started develop texts on risk analysis principles (…) The documents may be adopted by the Commission in 2007". This statement confirms clearly the EC position that such standards or guidance are absent in the relevant legal framework. The European Communities also notes the Codex reply "[no] standard *or related text*", which clarifies that there is absence not only of standards but also of guidelines and recommendations, in the sense of Articles 3 and 5 of the *SPS Agreement*.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) as defined by Codex and explain how they differ.

EC Comments

The European Communities has no specific comments other than to recall that its legislation, as applied to the six hormones, complies fully with the three components and actually goes further than the Codex work in progress. It is, however, true that there are some differences between the European Communities' and the US' and Canadian conception of these steps, as Drs. Cogliano and Guttenplan have explained in their replies, and the question is which philosophy will eventually prevail in the future work of Codex. The basic differences between the European Communities and the US and Canada reside, *inter alia*, in that the European Communities (i) is more strict with potentially genotoxic substances, (ii) does not always require a quantitative assessment of the risk (a qualitative assessment is acceptable when the data support it), (iii) pays more attention to scientific uncertainty and (iv) applies a higher level of health and environmental protection.

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

EC Comments

The European Communities has no specific comment at this stage other than to refer the Panel to its comments on question no 3 of the Panel experts questions.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? [see Canada's comments in para. 72 of its Rebuttal Submission]

EC Comments

The European Communities notes the reply of JECFA whereby "(…) most risk assessments of chemicals today on a national and international level are deterministic, i.e. they use a point estimate for the toxicological endpoint and a point estimate for the exposure assessment (…) this is (…) often a necessity due to the information at hand. Uncertainties around these point estimates should be considered in the risk assessment process. The current risk assessment process, which includes consideration of sensitive subpopulations, is considered to be sufficiently conservative to be public health protective." The European Communities also notes the reply whereby "(…) increasing efforts are under way (…) to explore methods to perform probabilistic risk assessment, i.e. include distributions rather than point estimates in the risk assessment process (...) however probabilistic methods in the toxicological assessment are not yet internationally agreed and are not yet commonly applied (…) the outcome of a probabilistic risk assessment is much more difficult to interpret and apply by risk managers." More important is JECFA's comment that: "(…) the probabilistic or deterministic approaches can be applied, independent if a compound is assumed to act via a threshold mechanism, i.e. non-linear, or not. JECFA's assessment process is based on the mechanism of action of the compound to be evaluated, non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect. In such a case, as for the hormones, a no-effect-level can be determined from which an ADI can be established."

These comments confirm the EC point that JECFA assumes non-linearity, but dos not look for it nor does it attempt to prove it. If JECFA's guess about the mechanism of action of the hormones is wrong, as the evidence submitted by the European Communities shows, then its assumption of non-linearity (on safe threshold) is obviously wrong. It is recalled again that in the 1999 assessment, JECFA concluded that oestradiol 17 β has "*genotoxic potential*", it found that progesterone "*on balance*" is not genotoxic, and that the evidence on testosterone was ambivalent. This shows that a slight error when JECFA draws its balance of the evidence can be catastrophic for human health, as its was with so many substances in the past, and most clearly with the evaluation of Carbadox referred to by the EC in its rebuttal submissions (at paras. 150-152 of US panel).

The Panel would have to understand that these comments by the European Communities are not trivial. Dr. Boobis (like JECFA) came to the conclusion that these hormones are not genotoxic on the basis of the so-called "weight of the evidence" approach, meaning that in their view the majority of the evidence does not yet accept that they are genotoxic by a direct mechanism of action, and this is because on their view there are not yet enough experiments *in vivo*. This, however, is disputed by the European Communities on the basis of evidence conducted both *in vitro* and *in vivo*.

Finally, JECFA states that in its reports and in the toxicological monographs on the safety assessment of the hormones it has"(…) used risk assessment principles particularly targeted to the evaluation of such substances (…) [and has considered] (…) other relevant toxicological end-points, such as reproductive toxicity, genotoxicity and potential carcinogenicity." The European Communities

contests the scientific accuracy and truth of this statement, because JECFA did not consider carefully many important end-points, such as the effects on pre-pubertal children, on the immune system, endocrinological effects, etc. The European Communities refers the Panel to the replies of Drs. Cogliano, Sippel and Guttenplan to the Panel questions in this regard.

Q8. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

EC Comments

The European Communities first likes to clarify that the question should have not asked whether there are "JECFA or Codex materials" but "JECFA or Codex materials that have been lawfully approved by the members of the Codex Alimentarius Commission". Furthermore, the European Communities considers that there is no reason to evaluate differently chemicals as opposed to biological or physical agents. The dose-response assessment can be done both qualitatively and quantitatively, if the data so permit. The European Communities has done a qualitative assessment in the case of these hormones. The difference is that JECFA based its findings on a no-effect-level only, whereas the European Communities found also that there is no safe threshold.

Q9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

EC Comments

The European Communities notes that the above definition from the 66 JECFA meeting, which covers also metabolites and associated impurities, was not the one followed when JECFA evaluated these hormones. Moreover, the definition of an ADI does not mean that there is no risk, as the defending parties and JECFA imply, but that there would be no "appreciable health risk". But whether the risk is "appreciable" or not is for each WTO Member to decide. This is precisely the function of its desired level of health protect which can be no (or zero) additive risk, and which is the level of protection applied by the European Communities in the case of these hormones when administered for animal growth promotion purposes.

Q10. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please also identify and describe any steps that are taken in the risk assessment process to build a margin of safety into to the final recommendation.

EC Comments

The European Communities notes that according to JECFA, "(…) in setting ADIs, an attempt is made to take account of special subpopulations that may be exposed." However, as the European Communities has shown, this is not properly done in the case of these hormones because the data used by JECFA for the endogenous production by pre-pubertal children are no longer valid. Moreover, JECFA states that it "(…) uses the risk assessment process when setting the ADI, i.e. the level of "no apparent risk" is set on the basis of quantitative extrapolation from animal data to human beings." This statement contrasts with its statement to the previous question, where it claims that it performed a qualitative assessment. In any case, whether qualitative or quantitative, JECFA did not use in all of

its calculations data from residues in meat from animals treated with these hormones for growth promotion purposes, as it is erroneously stated by the defending parties and the Codex and JECFA.

The European Communities also notes that JECFA "may recommend MRLs "not specified" or "unnecessary" when there is a wide margin of safety of residues when compared with the ADI (...)" and that "(…) JECFA may determine that MRLs cannot be recommended because of significant deficiencies in either residue data or available analytical methods or when an ADI is not established." It is crucial to note, however, that in the case of the three natural hormones JECFA did not specify MRLs because it found them "unnecessary". But this is utterly unscientific because there is no "wide margin of safety" for residues of these hormones given that it has been already established clearly that the endogenous circulating levels alone have been found to cause cancer for some individuals. It was, therefore, imperative for JECFA to evaluate the additive risk that the residues in meat from treated animals can pose to human health. This JECFA has failed entirely to do so, for the simple reason that there are currently no sufficiently powerful analytical methods to detect the origin of residues from the three natural hormones in meat, i.e. whether they are of endogenous or exogenous source. This is the only true reason for which JECFA did not specify MRLs in 1988 and in 1999, after it had found that an ADI had to be established. This is clearly stated in the 1988 evaluation of the three natural hormones by JECFA, where it is explicitly stated:

> "The Committee concluded that residues arising from the use of oestradiol-17β [and progesterone and testosterone] as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health. The Committee recognized that most methods of analysis for orstradiol-17β [and progesterone and testosterone] are radioimmunoassays, which usually have a large co-efficient of variation at the concentrations being measured. While these methods may be satisfactory for measuring oestradiol-17β [and progesterone and testosterone] levels in experimental situations, improvements would be needed if routine analytical methods for the control of residues were required. On the basis of its safety assessment of residues of oestradiol-17β [and progesterone and testosterone], and in view of the difficulty of determining the levels of residues attributable to the use of these hormones as growth promoters in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level [i.e. an MRL]" (see WHO Technical Report Series no 763, page 19, 1988).

However, this passage from the 1988 JECFA report on the three natural hormones has now mysteriously disappeared from the 1999 JECFA report on these hormones without any explanation, other than that there is now "a wide margin of safety". So, JECFA finds itself now in the paradoxical situation of having for the first time to establish ADIs for the three natural hormones but is not in a position to fix MRLs for their residues! And the explanation it has offered was to say that they are "unnecessary". But are they really "unnecessary", given the endogenous production levels by prepubertal children and the widespread misuse and abuse of these hormones found in the US and Canada?

The European Communities would suggest to the Panel to ask JECFA to clarify its position on these precise points.

Finally, it is also interesting to note that according to JECFA "[A]s a general principle, the Committee will not normally recommend an MRL that results in residue levels that lead to dietary intake exceeding the ADI based on toxicological or microbiological considerations." The European Communities has demonstrated that there is such a clear possibility of the ADIs being exceeded routinely. As the European Communities has explained in its Written Submissions, this has been explicitly recognised also in the US Carcinogenesis Report since 2002, and it is confirmed by the

replies of the experts to the questions of the Panel, in particular those of Dr. De Brabander and Dr. Sippel.

Q11. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

EC Comments

The European Communities notes that there is a wide discrepancy between the theory and reality, in particular given the narrow mandate of JECFA, the potentially subjective interpretation of the data, and the opaqueness of its procedures and the data it uses in its assessments. JECFA's reply does not convince because it does not provide the data upon which it based its assessment for verification and peer-review by independent scientists.

Q12. In paras. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

EC Comments

The European Communities notes that the replies of both Codex and JECFA confirm that the latter does not have the mandate to examine risk management options other than to propose or not ADIs and MRLs, and it has not been asked to consider such options when it examined these hormones. Moreover, both Codex and JECFA appear to have an extremely narrow understanding of what constitutes risk management: for instance, they appear to think that the question whether an identified (and characterised) risk is or is not "appreciable" is a risk assessment issue. This is not correct, as this issue is by definition a risk management question and it is a function of the chosen level of protection by the risk manager. A risk assessor's role, like that of JECFA, should be to identify only if there is a risk and to explain any scientific uncertainties that may surround its assessment. Its assessment of the risk may be qualitative or quantitative, but the decision whether a scientifically assessed risk (e.g. of cancer) is "significant" or "appreciable" is, strictly speaking, a risk management decision. It follows that JECFA does perform also risk management functions in the Codex system, despite its formal denial of doing so.

Q13. With respect to the data used in the evaluation of chemical substances, such as the hormones at issue, what are the data requirements for JECFA's work and how are they determined? Who provides data for such evaluations? Are any records/archives kept by JECFA? Do any confidentiality rules apply to data submitted to JECFA or should all data be publicly available? If confidentiality rules apply, in which circumstances? [see paras. 95-96 of EC Rebuttal Submission (US case), paras. 78-79 of EC Rebuttal Submission (Canada case), para. 123 of Canada Rebuttal Submission]

EC Comments

The European Communities would note the following statements by JECFA:

- "the data are mainly provided by companies who produce the compounds;

- the submitted data may be published or unpublished and should contain detailed reports of laboratory studies, including individual animal data;
- summaries in the form of monographs are helpful, but they are not in themselves sufficient for evaluation;
- the unpublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA;
- neither FAO nor WHO have facilities for storing printed data for long periods of time, so confidential data will either be returned to the submitter at the submitter's expense or destroyed after the evaluations have been completed;
- key material can be stored up to five years and will then be destroyed."

These statements confirm the EC position that JECFA has had access to the detailed reports provided by the industry, but failed to provide them to the European Communities. The European Communities has been asking for these confidential and unpublished data since 1999, so JECFA cannot pretend that it had destroyed them already at that time!

JECFA claims that "it is important to note that JECFA evaluations are completely publicly available, and a detailed description of the data evaluated is accessible through the monographs." But these monographs are not the original of the data used but processed and reworked information which does not enable scientists to verify the accuracy of the design of the study, of the experiments carried out, of the interpretations made and the conclusions drawn and for what reasons. The European Communities has not been asking for information regarding "the manufacturing process of substances, which are considered confidential for commercial purposes", but for the specific scientific studies (toxicological and residues analysis) in order to verify the scientific validity of these studies and the accuracy of the conclusions drawn by JECFA (and the defending parties). The European Communities has rendered public and provided its own studies to all the parties; therefore, it fails to understand why the US, Canada and JECFA (and Codex) continue to deny access to their own data.

The European Communities reiterates, therefore, its standing request to the Panel to order the production of their so-called confidential and unpublished data, if the credibility of their assessments and of this process is to be maintained. Otherwise it has to draw the necessary negative inferences from the failure to provide the requested data.

Q14. How are experts involved in JECFA's work selected? What are the selection criteria?

EC Comments

The European Communities simply notes that in the evaluation of the six hormones by JECFA have participated scientists who have no specific expertise on these hormones, like Drs. Boisseau and Boobis, since they have not worked on nor have published anything on these substances when used for animal growth promotion purposes. From the JECFA reply it is not clear to the European Communities whether the selection of JECFA's experts is as strict as that applied in the case of IARC (see its reply to Panel question no 22). The European Communities would ask the Panel to clarify further this point.

Q15. Please provide the definition of the term Good Veterinary Practice (GVP). Are there any relevant Codex standards, guidelines, or recommendations relating to GVP?

EC Comments

The European Communities notes that there is currently no definition nor guidelines on GVP in Codex and JECFA, as this is confirmed by the replies of Dr. Boisseau and Dr. De Brabander (question no 44 to experts).

Q16. Please provide an update on the status of international standards with respect to the six hormones at issue. What are the remaining procedures before the adoption of a standard on melengestrol acetate (MGA)? What is the timeframe for their completion?

EC Comments

The European Communities notes that the Codex standards on the five hormones were adopted by a very slim majority vote in Codex, despite the Codex' statement that decisions are taken by consensus. Indeed, the Codex standards were adopted in 1995 with 33 votes in favour, 29 votes against and 7 abstentions, that is by a minority of the members present and voting (see para. 4.77 of the 1997 Panel report, WT/DS26/R/USA, at page 39). Their assessment by JECFA dates of 1988. The Codex reply also confirms the EC position that currently there exists no standard for MGA.

Q17. Is the table in Exhibit CDA-32 outlining the chronology of JECFA's assessment of the hormones at issue and the resulting documentation complete?

EC Comments

The European Communities wishes to clarify that the 66th JECFA meeting (held 20 - 28 February 2006) deliberated on the MRLs previously proposed for melengestrol acetate. It did, however not consider any new data but limited itself to the correction of a calculation error. The EC highlighted this during the recent 16th Session of the CCRVDF that no original data were presented in the review (see ALINORM 06/29/31 paragraph 69).

Q18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

EC Comments

The European Communities notes the statement that "in the case of estradiol-17 beta, progesterone and testosterone, they were re-evaluated by the 52n JECFA (1999) at the initiative of the JECFA Secretariat", and that "the 12th CCRVDF (2000), in recognising that it had not requested the re-evaluation of the three substances and that the new MRLs recommended by the 52n JECFA did not differ significantly from the current MRLs, decided to not consider the new recommendation of the 52nd JECFA." There are many comments one can make on this statement. First, it is quite unusual for substances to be re-evaluated at the request of JECFA's Secretariat, despite the written request of one of its members (who represented at the time 15 countries) to postpone the re-evaluation for a couple of years in view of the expected new evidence that was about to become soon available. Indeed, most of the new evidence generated by the European Communities became available between 1999 to 2002. The European Communities would like to ask JECFA if this has ever happened in other cases. The European Communities has never understood what would have been the problem if its request for postponement were taken into account.

The European Communities notes that JECFA and Codex do not reply to the second part of the question. In any case, it is surprising that the same JECFA Secretariat, which used to be common with

that of Codex, is now not proposing to review again these hormones, despite the wealth of the new evidence that became available from so many sources and the standing request by the European Communities.

It is also noteworthy that the CCRVDF did not adopt the 1999 assessment of the three natural hormones by JECFA, which may mean that this 1999 assessment is of no relevance for the purposes of these disputes.

As regards MGA, the European Communities has requested its re-evaluation on the basis of more recent scientific evidence.

Q19. What would be the procedures for requesting JECFA to re-evaluate its recommendations in light of new concerns/evidence? How would an amendment be adopted? Has the European Communities approached JECFA for this purpose with respect to the hormones at issue in this case? [see Exhibit EC-63]

EC Comments

The European Communities notes the statement by JECFA that the "European Union has not asked the JECFA Secretariat to bring their data referred to in the report of the 11th session of CCRVDF (see below point 1 of question 20) before JECFA for review." This is not correct because there is a standing EC request to review the hormones on the basis of the latest information available, including that generated by the European Communities.

Q20. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones, which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by CCRVDF? What is the status of these recommendations? [see para. 96-97 of EC Rebuttal Submission (US case), para. 79-80 of EC Rebuttal Submission (Canada case)]

EC Comments

The European Communities refers the Panel to its submissions and in particular Exhibit EC-63, which provides a more detailed account of the events with precise references to the original letters. It is unfortunate that JECFA states that it "decided to re-evaluate previous assessment when the Committee is made aware that there is new data which may be pertinent to the risk assessment of the substances in question", but failed to wait for the most important part of these data to become publicly available.

The European Communities draws the attention of the Panel to the statement that "most of the studies were the same", which confirms the EC position. The European Communities also notes that "a complete dossier submitted to the US Food and Drug Administration" was provided and that the "FDA kindly permitted the FAO expert to the Committee to search all their relevant files for data." This statement confirms again the EC position that the US and JECFA could have provided the same data also to the European Communities as it has been consistently requesting.

JECFA states that it performed "a more detailed thorough review of the validity of the analytical methods used in the studies and used only data generated using valid methods. It also performed more detailed statistical and graphical analyses of the data." However, since most of the data were the same old data, one wonders what kind of thorough processing JECFA now did, which it had failed to do in

its 1988 assessment of the same data. This is all the more crucial given that the data in question are unpublished data of the 1970s. The European Communities recalls that this so-called "thorough review" seems to have been performed by Dr. Arnold, who has himself declared to this Panel during the selection procedures that he believes eating meet treated with these hormones poses "no increased health risk for consumers".

JECFA also states that "a few additional investigational studies were also reviewed", but it does not explain which ones and how important they were for its assessment. JECFA further states that "since the FAO FNP 41/12 monograph provides all raw data used (in graphical form) and all the calculations performed, the document is also more transparent than the corresponding monograph produced by the 32nd Meeting". The European Communities reiterates that it precisely has been claiming for transparency in the JECFA proceedings, and a graphical presentation of the same old data is not what one would normally understand by transparency.

JECFA states that "this conclusion was based on studies of the patterns of use of estradiol for growth promotion in cattle, the residues in animals, analytical methods, toxicological data from studies in laboratory animals, and clinical findings in human subjects." The European Communities disputes that such detailed studies have been performed and reiterates its standing request to be given access to these data or to be made available to the Panel and its experts for review.

JECFA further states that "at its 52nd meeting in 1999, estradiol-17β was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-50 ng/kg bw on the basis of the NOEL of 0.3 mg/day (equivalent to 5 μg/kg bw per day) in studies of changes in several hormone-dependent parameters in postmenopausal women. A safety factor of 10 was used to account for normal variation among individuals, and an additional factor of 10 was added to protect sensitive populations." This confirms that (i) JECFA did not consider residues in meat from animals treated with these hormones for growth promotion purposes, (ii) it based its ADI on "changes in several parameters in postmenopausal women" but not on the much lower rates of prepubertal children (as did the European Communities), and (iii) it sought to address these problems with the application of safety factors!

The European Communities notes that statement of JECFA that "the 52nd JECFA performed a detailed theoretical intake assessment based on a worst case scenario (all animals are slaughtered at the time of the highest hormone levels - this time point differs largely from the time point at which the benefit due to the anabolic effect is greatest). In this assessment intake estimates for preferential meat eaters were performed on the basis of the hormone levels of treated animals in comparison with the corresponding levels in untreated animals and the additional "burden" or "excess intake" was calculated. For total estrogens the highest excess intakes from approved uses calculated this way were in the order of magnitude of 30 – 50 ng/person/day. This range of intake is less than 2% of the ADI for estradiol-17β established by JECFA at the 52nd meeting. For certain experimental studies carried out with experimental combinations resulted in an excess intake of around 4% of the ADI." The European Communities would like to see the original of these underlying data, as the similar or more detailed studies and experiments in has generated itself provided different and in many cases much higher values (see e.g. Exhibits EC-16, 17, 18, 19, 34, 47, 52, 53 and 78). The same applies for testosterone and progesterone.

JECFA states that "hormone concentrations found in individual populations of treated animals, although they were typically statistically significant higher than untreated controls, were well within the physiological range of these substances in bovine animals. The data assessed and the worst case scenario calculations made indicated a wide margin of safety of consumption of residues from animals treated in accordance with good practice of use of the veterinary drugs containing the hormones in question. JECFA therefore concluded that there was no need to specify numerical

maximum residue levels for the three hormones and recommended MRLs not specified in bovine tissues." This is an important statement that needs to be factually substantiated. The European Communities notes that the hormone concentrations found in treated animals were significantly higher than in untreated animals.

As for the reasons for which JECFA established in 1999 ADIs, the European Communities notes the statement that this was due to "the additional data reviewed and the need to establish an ADI as quantitative estimate for a safe oral intake. The exposure assessment performed would then allow the comparison of the estimated intake with the ADI." Thus, this confirms the EC position that it was the new evidence showing risk of cancer that led JECFA review its 1988 assessment. And if JECFA postponed its assessment until the new and more recent data generated by the European Communities were taken into account, it could have reached still another and arguably more accurate conclusion. In any case, it is clear that in 1999 JECFA did not establish ADI in order explain better its evaluation, as it is claimed erroneously by Dr. Boisseau (see his reply to Panel question to the experts no 18).

JECFA states that "sufficient new data from observations in humans were available to the 52nd JECFA which were suitable to derive ADIs." The European Communities does not know and has not seen these "data from observations in humans" and, if they exist, they are certainly different from the data it has generated itself with its own studies. JECFA should therefore provide them to the parties, the Panel and its experts for review. Moreover, the so-called "wide margin of safety" claimed by JECFA to exist is no longer credible in view of the "significantly higher levels" identified in treated animals and the need to establish ADIs, not to mention their direct genotoxicity and the other adverse effects established by the European Communities. Furthermore, the EC scientists rightly question why MRLs were not established in 1999, given that JECFA had felt nevertheless the need to establish ADIs. Was it for the alleged "wide safety margin" or simply because "of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle", as JECFA had admitted in 1988? But if the latter was the real reason, this means that JECFA did not carry out a quantitative dose-response assessment of residues in meat from treated animals under realistic conditions of use, as it is argued by the European Communities.

Q21. What is the mandate of the International Agency for Research on Cancer?

EC Comments

The European Communities has no specific comment at this time.

Q22. Who are the members of the IARC?

EC Comments

The European Communities has no specific comment at this time.

Q23. What are IARC Monographs? How are they prepared?

EC Comments

The European Communities notes the IARC statement that "when the epidemiological evidence is *sufficient*, the final evaluation is *carcinogenic to humans*, regardless of the experimental evidence. In other cases, the mechanistic and other relevant data are considered to determine whether the default evaluation should be modified, upwards or downwards. A subgroup of experts in cancer mechanisms assesses the strength of the mechanistic data and whether the mechanisms of tumour formation in experimental animals can operate in humans. The overall evaluation is a matter of scientific judgement, reflecting the combined weight of the evidence."

The European Communities would like further clarifications on the following points: Does the above statement mean that a substance can be classified in Group 1 even if there are no or a limited number of experiments showing genotoxicity in vivo? Moreover, in which of the different groups are genotoxic substances classified? How does IARC define genotoxic substances?

Q24. Please briefly explain the groupings that are used to categorize "potentially carcinogenic agents"? What are the implications when an "agent" is placed in one of the IARC categories?

EC Comments

The European Communities would like to request the following clarifications: 1) Would the IARC describe its assessments as risk assessments or as assessments that also include risk management? 2) When a substance is placed in Groups 1, 2A and 2B, what is the majority of IARC's members normally expected to do? To authorise or prohibit the substances in question? On what else does their decision depend? 3) Is the assessment performed by IARC a qualitative or a quantitative assessment of potential risk? 4) Is the IARC classification of various groups based on dose-response estimations under realistic conditions of use of the various substances? 5) Is the classification based only on experimental data in animals and extrapolations to humans or do they include also data from residues which such substances may leave in food?

Q25. Which of the six hormones at issue in this dispute (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate) have been evaluated by the IARC? Have any specific risks from the consumption of meat from cattle treated with these growth promotion hormones been assessed by the IARC?

EC Comments

The European Communities notes the statement that "Trenbolone acetate, zeranol, and melengestrol acetate have not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with these growth promotion hormones", and would like the following clarifications: 1) Does it mean that IARC's evaluation of the three natural hormones covers also the specific risks from the consumption of meat from cattle treated with those hormones for growth promotion? 2) Can the IARC be more specific on the last part of the question? 3) Is it possible a pharmacologically active substance that is classified in Group 1 to ever lead residues in food of this substance to be classified into a different category? 4) If so, under what conditions can this take place?

Q26. How does the work of the IARC feed into the work of national regulatory agencies or international bodies, in particular with respect to assessments of risks from the consumption of meat from cattle treated with the six growth promoting hormones at issue in this dispute?

EC Comments

The European Communities would like IARC to clarify what it means by "as scientific support for their actions"? Does it mean that they can be used as risk assessments? Are they normally scientifically complete and adequate to be used as risk assessments? Could IARC be more specific and reply to the last part of the question concerning the consumption of meat from cattle treated with the six hormones or at least for the three hormones that it has assessed and classified?

ANNEX F-3

COMMENTS BY THE EUROPEAN COMMUNITIES TO THE COMMENTS BY THE UNITED STATES AND CANADA ON THE REPLIES OF THE SCIENTIFIC EXPERTS TO QUESTIONS POSED BY THE PANEL

(12 July 2006)

Introduction and general comments

1. The European Communities thanks the Panel for the opportunity to comment on the other Parties' comments on the Panel's experts' replies. Before setting out its comments the European Communities would like to make two preliminary remarks of a general nature.

2. First, the European Communities notes that the United States, in its comments, has chosen to follow its own structure in what may well be considered a full-fledged additional submission. Apart from the fact that reference is made to legal claims which the United States has not made anywhere (e.g. Article 5.6 of the *SPS Agreement*, see paragraph 5 of the US submission), the European Communities considers that this approach is confusing and of little assistance to the Panel and its experts as well as to the other parties. It is not surprising that the US has resorted to this tactic, as the replies of the majority of the experts support the scientific evidence and the arguments of the European Communities.

3. In order to facilitate a structured debate, the European Communities will try to disentangle the misleading comments made by the United States. Also, for the same purpose, the European Communities makes but one set of comments, which addresses the Canadian and (as best as possible) the US comments following the order of the questions as asked by the Panel to the experts and the international bodies.

4. Second, in light of the other Parties' comments on this general issue, it seems appropriate to briefly come back to the role of experts in these panel proceedings. As the European Communities has pointed out in earlier submissions (in particular in its submission of 15 March 2006), the purpose of the scientific questions and the role of the experts is to help the Panel understand the scientific issues involved. Neither the Panel nor the experts should aim to conduct their own risk assessment or to conduct a *de novo* review of the sanitary risks identified by the European Communities. The task of the scientific experts is to assist the Panel in assessing whether the scientific basis of the measure taken by the European Communities complies with the recommendations and rulings of the DSB in the *EC – Hormones* case. But the experts should not make comments on risk management options, since this is not their expertise or role. Therefore, the focus of the scientific questions should be to help the Panel understand the risk assessment conducted by the European Communities since the adoption of the Panel and the Appellate Body reports in 1999. Unfortunately, as the European Communities has demonstrated by its comments of 30 June 2006, the replies of Dr. Boisseau and Dr. Boobis have not always complied with the above requirements.

A. GENERAL DEFINITIONS

Q1. Please provide brief and basic definitions for the six hormones at issue (oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate), indicating the source of the definition where applicable.

5. The United States and Canada have not referred to or commented in substance on the experts' (Drs. Boisseau, Boobis and Guttenplan) replies to this question.

Q2. Please provide definitions for the following terms as they relate to the hormones at issue, indicating the source of the definition where applicable: anabolic agents, steroids, steroidal oestrogens, parent compounds/metabolites, catechol metabolites, mitogenicity, mutagenicity, androgenic/oestrogenic activity, genotoxicity, genotoxic potential, carcinogenicity, and tumorigenicity. In your replies, please be sure to identify and describe any relevant differences between the terms.

US comment

6. The United States has not referred to or commented on the experts' (Drs. Boisseau, Boobis and Guttenplan) replies to this question.

Canada's comment

7. The comments by Canada (at paras. 8-9) are not accurate. The statement that a substance (in this case oeastradiol-17β) "has genotoxic potential" does not mean that there is a "statistically likelihood" that it is carcinogenic (this is not what the European Communities has argued) but that on the basis of the evidence available, in particular *in vitro* studies, the genotoxicity of the substance is possible. This is not a theoretical statement but a frequent conclusion scientists make for this type of substances. In addition, in this case there is also *in vivo* evidence supporting that statement. Dr. Boobis and Canada may not like this evidence or would like to see more *in vivo* evidence before they are convinced, but this is irrelevant. The European Communities is entitled to rely on this recent and credible evidence if necessary to achieve its level of health protection.

B. RISK ASSESSMENT TECHNIQUES

Q3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

US comment

8. The US comments on Question 3 are contained in paragraph 13 of its submission. The European Communities notes that there is general agreement among the parties that there is no internationally agreed risk assessment technique, within the meaning of Article 5.1 of the *SPS Agreement,* for the assessment of these hormonal substances. It is equally uncontested by all that there exists a number of documents which represent at most a practical understanding among some international experts on certain principles. These documents do not have any legal value under the *SPS Agreement* since they are not "risk assessment techniques developed by the relevant international organisations." In any event, the European Communities notes that neither the US nor the experts claim that the European Communities has not followed these.

Canada's comment

9. Canada's comments (in particular at paras. 14-15) do not accurately describe the legal relevance of the documents to which it and JECFA have referred to. Canada states that many of the risk assessment techniques and methodologies "are also relevant to the risk assessment of veterinary drugs". However, these are no risk "assessment techniques" in the first place, in the sense of Article 5.1 of the *SPS Agreement* and, secondly, they cannot be applied by analogy to other kind of substances than for those for which they have been foreseen.

Q4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological

assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)].

US comment

10. The US comments on the experts' replies to this question are contained in paragraph 13 of its submission. As stated above, these documents reflect the general discussion in the absence of an internationally agreed risk assessment technique and the presence of certain guidance documents. However, the United States misquotes Dr. Boisseau when pretending that he was referring to the "assessment of such drugs "[i.e. the hormonal substances in question] when stating that "it has been internationally harmonised through scientific conferences …". Dr. Boisseau was not referring to the assessment as such, but to a "general rationale" on that assessment. Indeed, if there is some understanding among certain scientists on a general way of conducting a risk assessment, the European Communities applies this as much as any other country.

Canada's comment

11. Canada maintains that, despite of the accuracy of the relevant EC statement "any suggestion that relevant risk assessment techniques or guidance developed by international organizations for the conduct of veterinary drug risk assessments do not exist is baseless".

12. In the European Communities' view, Canada is misinterpreting the replies of Dr. Boisseau and Dr. Boobis. First, it should be underlined that both experts (and in addition Dr. Guttenplan) have confirmed the accuracy of the EC statement. Second, the existing general JECFA guidelines to which Drs. Boisseau and Boobis refer can not be taken – as Canada does – as a replacement of an international detailed Codex standard which alone would be of legal relevance under the *SPS Agreement*.

13. JECFA might have produced certain internal guidelines on risk assessment for certain substances. However, it is a totally different matter to elevate internal JECFA papers, which have never been approved by Codex Members, into the rank of an international standard. Thus, Canada's insinuation and interpretation of the replies by Dr. Boisseau and Dr. Boobis is inaccurate and unacceptable.

Q5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) and explain how they differ.

US comment

14. The United States has not provided comments on the experts' (Drs. Boobis, Boisseau, Cogliano, Guttenplan) replies to this question.

Canada's comment

15. In summarizing the experts' replies, Canada reproduces Dr. Boobis' response and presents this as the common denominator of the experts. However, there are differences. For instance, in respect of the "risk assessment" Dr. Boobis introduces a concept of the "weight of evidence", which is not found in the replies by Dr. Boisseau, Dr. Cogliano or Dr. Guttenplan. These experts rather emphasize the risk assessment as an evaluation of risk (Dr. Guttenplan), a description of the "adverse effects of exposure of hazardous agents (Dr. Cogliano) or the "likelihood and the gravity of any unexpected unwanted effect for the consumer" on the basis of "scientific date, relevant with regard to assessing this risk" (Dr. Boisseau).

16. These differences are important since Dr. Boobis' reply, which obviously suits Canada best, implies a margin of discretion in (or balancing and weighing of) the scientific risk assessment procedure, based on the "weight of evidence", which is not the case for the other experts.

17. Furthermore, as regards the risk management step, Canada again uses the language of Dr. Boobis reply and tries to "present" it as the common view of all experts. This is, in particular, interesting since Dr. Boobis refers in this context to "ensuring fair trade" which is not mentioned by any of the other experts. Instead, these experts refer to the use of other scientific criteria such as "economical, sociological, cultural" (Dr. Boisseau) or "legal mandates, technical feasibility, cost, equity, and social norms" (Dr. Cogliano). This is an interesting difference, because the concept of "fair trade" is not clearly defined and Canada and Dr. Boobis may have a different interpretation of this concept than for instance the United States, the European Communities or other experts.

18. Moreover, Canada claims that all experts appear to support the so-called "functional separation" between risk assessment and risk management (at para. 20). Even if this were so, *quod non*, this is irrelevant for the *SPS Agreement*, because the Appellate Body has interpreted correctly its provisions in the 1998 *Hormones* case to partially overlap (at para. 181 of its report).

Q6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

US comment

19. The United States refers to the experts' replies on this question in paragraph 14 of its submission trying to make again the erroneous point that the European Communities risk assessment did not engage in a hazard characterization because it did not evaluate a dose-response relationship. This is discussed in more detail below under Question 11.

Canada's comment

20. Canada's summary of the experts' replies (Drs. Boisseau, Boobis and Guttenplan) concerning "hazard identification" is not accurate. According to Canada, "the experts" agree that hazard identification "involves the determination of *whether* an agent has the potential to cause adverse effects" (Emphasis added). However, this is not what Dr. Boisseau, Dr. Boobis and Dr. Guttenplan say. All of them do not define this step as to "whether" or not there are adverse effects. Rather, Dr. Boisseau, Dr. Boobis and Dr. Guttenplan define hazard characterization in respect of the identification of the different elements causing adverse health effects in humans.

21. In respect of the "hazard characterization" it is not true, as Canada summarizes it, that all experts refer in their definition to a "dose-response assessment" or the determination of thresholds, i.e. an NOAEL or an ADI. Indeed, Dr. Guttenplan merely refers to the "quantitative and/or qualitative evaluation of the nature of the adverse health effects associated with the hazard" without referring to a dose-response relationship or the establishment of whatever threshold. But even Dr. Boobis or Dr. Boisseau clearly condition the dose-response threshold aspects to "whether or not this is possible". Consequently, Canada's implied conclusion that these elements form an "integral part" of the risk assessment which the EC failed to complete are a serious mischaracterization of the experts' replies.

22. As regards the definition of the "exposure assessment" Canada, again, does not provide a proper summary of the experts' replies even though it pretends that all experts have the same view. Canada uses the words of Dr. Boobis to define the exposure assessment as a step to evaluate

"quantitatively" the exposure of consumers to veterinary drugs.[1] However, Dr. Boobis and Dr. Guttenplan refer explicitly not only to the quantitative aspects, but also to the "*qualitative* evaluation of the likely intake".

23. In respect of the "risk characterization" Canada again generalizes from one expert reply and presents them as a common reply of all experts. This is obvious when Canada quotes Dr. Boisseau's statement whereby risk characterization "is not to assess qualitatively and quantitatively the likelihood and gravity of the adverse effects of consumers (…) but to protect consumer's health from any adverse effect associated with residues". In this context, Canada also pretends that all experts confirm that an MRL would be established. This presentation is simply wrong. In fact, neither Dr. Boobis nor Dr. Guttenplan refer to the "protection of consumer health from any adverse effects" and to the establishment of MRLs. Rather, both experts limit themselves to the qualitative and, where possible, quantitative determination, including attendant uncertainties, of the likelihood of occurrence or severity of potential adverse health effects. It follows, therefore, that Dr. Boisseau's reply contains a subjective judgement and a procedural step which is not supported by Dr. Boobis and Dr. Guttenplan, contrary to what Canada pretends. Moreover, Canada persists in its error to consider that it is the "probability" of occurrence of the adverse effect that counts, when the Appellate Body has clarified in the *Hormones* case that it is not the probability but the likelihood (or possibility) that is meant by Annex A(4) of the *SPS Agreement*.

Q7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations, in your view, addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? Have they been addressed in the 1988 and 1999 JECFA risk assessments of these hormones? [see Canada's comments in para. 72 of its Rebuttal Submission]

US comment

24. The United States refers to the experts' replies to this question in paragraphs 15, 16 and 17 of its submission. Here again the US refers selectively to the "experts" views, when only Drs. Boisseau and Boobis appear to support what the US is arguing. Moreover, the basic error of these scientists, of the US (and Canada for this matter) and of JECFA is that they all argue that oestradiol is not genotoxic but acts only through hormone-mediated receptors. On the basis of this erroneous assumption, based on old and outdated data, they all come to the conclusion that there is a threshold dose below which there was no appreciable risk over a lifetime of exposure.

25. This kind of statement by the US is surprising given that its own scientists no longer agree with this assertion. The US Carcinogenesis Report since 2002 has classified oestradiol as a proven human carcinogen (see Exhibit EC-101). Indeed, the above US report states *inter alia*:

> "The evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor. *In addition, there is evidence that other mechanisms may play a role in the carcinogenic effects of estrogens in some tissues.* Prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. *Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and*

[1] Canada and Dr. Boisseau, however, differ on the food basket which according to Canada contains 300g muscle, whereas Dr. Boisseau refers to 500g muscle.

> *possibly direct and indirect genotoxic effects.* The relative importance of each mechanism is likely a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state (Yager and Liehr 1996)." (emphasis added)

It is clear from the above excerpt that all the relevant US scientific institutions that have collaborated in the preparation of this Report have come to the conclusion that oestrogen acts not only through the estrogen receptors but, in addition, also by "other mechanisms". The report states also that "the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects". This finding was made for the first time in the 2002 Report and is being repeated ever since. It is very strange that neither Dr. Boisseau nor Dr. Boobis commented on this, and it is even stranger that neither of the defending parties have ever said something about this, which clearly supports the EC assessment on this crucial point. Indeed, the European Communities is not doing other than what Dr. Boobis has described in his reply to Question no 7, namely that: "In practice, it is likely that as veterinary drug residues in food are avoidable by not using the drug, the Committee would have declined to establish an ADI".

Canada's comment

26. The European Communities is again opposed to Canada's selective perception of the experts' replies. Canada merely pretends that "the experts confirm that JECFA was aware of "non-linear situations" and took these into account in conducting its risk assessment for the hormones at issue".

27. However, Dr. Boisseau's reply is more nuanced than Canada would like to see. Dr. Boisseau replied that JECFA was aware in 1987 of non-linear situations but this was a general comment. In its reply, Dr. Boisseau only exemplifies this general awareness in respect of specific substances which are unrelated to the hormones in dispute and where at the time, JECFA concluded not to establish an effect-dose relation or to recommend an ADI.

28. Yet, in respect of oestradiol-17β, Dr. Boisseau expressly states that "in its 32nd session held in 1987, JECFA did not address this kind of non-linear situation for oestradiol-17β (…)". Similarly, in 1999, according to Dr. Boisseau, JECFA "did not take into account consideration a non-linear situation in its risk assessment (…)". Against this background, Canada's presentation of Dr. Boisseau's reply on non-linear situations is unsustainable.

29. Canada finds support in the statement of Dr. Boobis. But his statement and that of JECFA are scientifically unsound for the reasons already explained by the European Communities. Canada claims (at para. 31) that the European Communities has presented no evidence; however, this is not true because the evidence is there but Canada chooses to ignore it. For instance, Canada did not comment so far on the 2002 US Carcinogenesis Report quoted above.

Q8. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please identify and describe any steps that are taken in the risk assessment process to build a margin of safety into the final recommendation.

US comment

30. The United States does not refer to or comment on the experts' replies to this question nor to JECFA's and Codex replies to the same question (question 10 in questions asked to Codex, JECFA and IARC).

Canada's comment

31. Canada's description of the expert replies demonstrates again a lack of precision and accuracy. Canada, for instance, refers to Dr. Boobis answer (to Question 54) that an ADI is a threshold "that will pose zero risk" to human health. However, in this reply, Dr. Boobis only refers to a WHO definition of an ADI whereby there would be "no appreciable risk with daily exposure over a lifetime". It goes without saying that the difference of "no risk" and "no appreciable risk" is considerable since the latter one involves a subjective judgement. Indeed, what may be "appreciable" to somebody may not be "appreciable" to others. Yet, in this sensitive hormones' discussion, these fine differences make a difference. This is an issue of risk management, not of risk assessment, in the sense that Dr. Boobis cannot decide for the democratically elected governments in the European Communities what risk is "appreciable". It is, therefore, necessary to make the Panel aware of such rather blunt presentations of the experts' replies by Canada. Indeed, Canada is confusing its own subjective (policy) judgements with the remarks of the scientific experts.

32. It may not come as a surprise that Canada's description regarding the experts' replies on MRLs is also misleading. First, it is inaccurate to say that "the experts have confirmed that the MRL is a management tool (…)" and that "if residues are within the MRL, then the ADI is unlikely to be exceeded and no adverse effects to human health are to be expected". First, only Dr. Boisseau refers in its answer to MRL but not the other experts. Second, Dr. Boisseau clearly states that a MRL is "an operational tool which offers a practical way to be sure that this ADI will not be exceeded". Conversely, contrary to what Canada describes Dr. Boisseau does not say "no adverse effects to human health are to be expected". Rather it appears that at this stage one would have to go back to the discussion whether an ADI poses "no risk" or "no *appreciable* risk". Moreover, Canada states (at para. 36) that JECFA has built into its calculations large safety margins. However, none of the points made by Canada here is correct, at least not in the case of these hormones. First, because JECFA did not consider all the metabolites for instance of oestradiol, like the esters. Indeed, *Maume et al.* have confirmed the presence of estradiol **esters** in meat of treated animals in an order of magnitude not very different to the free estradiol residues. But the estradiol esters is a totally new class of residues that have not been considered before in any risk evaluation. Their potential bioactivity may be much higher than the bioactivity of estradiol as such. The recent data provide clear evidence (1) for their existence after application of estradiol to cattle and (2) for their elevated oral bioactivity. Undoubtedly, these are important new data, and an accurate evaluation of the risk originating from steroid hormone esters will only be possible, if many more data become available. This includes the additional need to look for trenbolone esters and their bioactivity. (see *Maume D, Deceuninck Y, Pouponneau K, Paris A, Le Bizec B and Andre F (2001): Assessment of estradiol and its metabolites in meat, APMIS, **109**:32-38*, Exhibit EC-47*)*. Second, because the bioavailability of these hormones has been seriously underestimated, and thirdly, because the so-called food basket can easily lead to residues intakes that by far exceed the endogenous production of these hormones, especially by pre-pubertal children.

Q9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

US comment

33. The United States refers to Drs. Boisseau's and Boobis' and to JECFA's replies to this question in paragraph 17 of its submission.[2] The US approves the statement by Dr. Boisseau about the quality and the quantity of the data used by JECFA. However, this is not surprising because the data

[2] Question 11 in questions asked to Codex, JECFA and IARC.

used by JECFA are too old. Conversely, the data used by the European Communities are more recent and converge on this point with the statement of the US Carcinogenesis report which states that "… Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects ...". Thus, there is no doubt that there are several gaps in our knowledge but the new evidence available confirms the direct and indirect genotoxicity of oestradiol and of the other hormones.

Canada's comment

34. Canada draws conclusions from JECFA's replies which are plainly wrong. JECFA was making a general and abstract statement on this point, but this tells us nothing of whether the ideal situation described in its reply is applicable in the case of these hormones, because JECFA's evaluations date from 1988 and are too old by today's scientific evidence.

Q10. In para. 129 and 168 of its Replies to the Panel Questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not". Does Codex have risk management options other than (1) the establishment of an MRL, (2) establishing that an MRL is not necessary or (3) no recommendation?

US comment

35. The United States does not refer to or comment on Dr. Boisseau's and on Codex' and JECFA's replies to this question.[3]

Canada's comment

36. The European Communities observes that, like the question itself, Canada's comments are confusing again what is a risk management measure in the terminology of Codex Alimentarius and JECFA and what this term should be understood to include in the *SPS Agreement*, as interpreted by the Appellate Body in the *Hormones* case.

Q11. What should, in your view, be the components of a qualitative risk assessment, compared with a quantitative risk assessment? [see para. 82 of Canada Rebuttal Submission]

US comment

37. The United States does not refer to or comment on the experts' (Drs. Boisseau, Boobis, Cogliano) replies to this question.

Canada's comment

38. Canada draws (at paras. 42-43) from the replies of the two scientists (Dr. Boisseau and Dr. Boobis) to this and to subsequent questions the conclusion that a risk assessment that does not include a dose-response assessment would be incomplete. However, as the other scientists who replied to these questions have explained, the European Communities has performed a qualitative (and where possible a quantitative) dose-response assessment. Moreover, Canada criticises (at para. 43) the relevance of the monographs produced by the IARC as a basis for conducting a dose-response assessment and cites in support the 1998 Appellate Body report in the *Hormones* case. However, the statement by the Appellate Body quoted by Canada is partly incorrect and partly irrelevant today. It is

[3] Question 12 in questions asked to Codex, JECFA and IARC.

incorrect because the evaluation of substances by IARC, like the three natural hormones, have served for so many years responsible governments in their risk assessments and it is simply inaccurate and scientifically unsound to suggest that they do not provide a sufficient basis for a risk assessment. This is because the toxicological and other scientific evidence on which both the JECFA and the IARC base their findings is the same: they both decide on the carcinogenicity of a substance on studies conducted *in vitro* and *in vivo* and extrapolate from animal models to humans (if there is no direct evidence from experiments on humans). There is nothing in the JECFA data base and the methodology used by it which is different from the data on carcinogenicity and the methodology used by IARC. This is very important to understand. If there are residue data from meat treated with these hormones for animal growth promotion, IARC will use them in the same way as JECFA normally does. The difference is that JECFA has come to the conclusion that the three natural hormones are not genotoxic, which is not the conclusion reached by IARC on the basis of broadly the same toxicological evidence. But once JECFA had reached the conclusion that there is a safe threshold, it then used the residues data from treated meat in order to see if the presumed safe theoretical threshold would be exceeded. This, the IARC did not have to do, as the other direct and indirect evidence it examined supported the characterisation of these hormones as proven human carcinogens. Moreover, the most recent data cited and used by the European Communities and also those cited (for the first time) in the 2002 US Carcinogenesis Report confirm that oestrogen is genotoxic by direct and indirect mechanisms of action. Therefore, the data from residues in treated meat, to which para. 200 of the 1998 Appellate Body report refers, are irrelevant.

39. It should however be stressed that, in any case, the 1999, 2000 and 2002 risk assessment conducted by the European Communities were based also on residues in meat treated with these hormones for animal growth promotion purposes, which were generated under realistic conditions of use, that is where GVP is respected but also where abuse or misuse could occur. These studies have shown that the resulting residues in treated meat are by far higher than the residue levels considered by the old and outdated studies on which the defending parties and JECFA based their findings. Moreover, the intake of residues from treated meat consumed by prepubertal children would exceed the ADIs and MRLs established by JECFA if the much lower levels of endogenous production of the three natural hormones is taken into account. That is why the European Communities considers imperative that these old data and the methods by which they have been measured and assessed should be provided to this Panel, its experts and the European Communities for a review. It is only then that a proper conclusion could be drawn on the accuracy and relevance of these old data for the risk assessment.

Q12. How is scientific uncertainty addressed in risk assessments in general? With respect to the assessment of risks from the consumption of meat treated with the growth promotion hormones at issue, how has scientific uncertainty been considered by JECFA/Codex ? How does it differ from the way it has been considered by the European Communities in its assessment of risks from the consumption of meat treated with the growth promotion hormones at issue?

US comment

40. The United States while referring to Dr. Boobis' reply to this question in paragraphs 17 and 20 of its submission[4] does not discuss or comment the issue of scientific uncertainty.

Canada's comment

41. Canada makes again (at para. 46) the irrelevant argument that the European Communities is not consistent because it prohibits hormone-treated meat but allows the consumption of foods (e.g.

[4] There is no reference to Dr. Boisseau's reply to the same question.

milk, eggs, meat) containing some of these hormones at levels many times higher. But this argument has been made by both parties before the 1997 panel and has been rejected clearly by the Appellate Body in the 1998 Hormones report (at para. 221) as "an absurdity". So the European Communities wonders why Canada keeps repeating it.

C. ASSESSMENT OF OESTRADIOL-17B

Q13. To what extent, in your view, does the EC risk assessment identify the potential for adverse effects on human health, including the carcinogenic or genotoxic potential, of the residues of oestradiol-17β found in meat derived from cattle to which this hormone had been administered for growth promotion purposes in accordance with good veterinary practice? To what extent does the EC risk assessment evaluate the potential occurrence of these adverse effects?

US comment

42. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan) replies to this question in paragraphs 19, 20, 21, 32, 37 and 84 of its submission. However, the underlying theme in all US comments is the fundamental error that these hormones, and in particular oestradiol 17β, are not carcinogenic because a safe threshold exists. This is a fundamental error on which the European Communities has already commented above (e.g. to Question no 7).

Canada's comment

43. Canada's statement that the replies by Dr. Boisseau, Dr. Boobis and Dr. Guttenplan all indicate that the EC risk assessment "was deficient in one manner or another in its evaluation of the potential occurrence of adverse effects" is a very unqualified summary. In particular, Dr. Guttenplan has expressly stated that the European Communities has done a "thorough job in identifying the potential adverse effects on human health of oestradiol-17β" and that the European Communities has "performed thorough studies of residues levels in cattle, and the environment". Most importantly, Canada states (at paras. 49-51) that "there is no evidence that this [genotoxic] potential is realized in vivo (as opposed to in vitro)", that Dr. Boisseau disagrees with the European Communities "as do most other experts and international scientific bodies", and that the European Communities decision not to conduct a complete risk assessment "is not supported by the evidence". None of these statements is correct. The European Communities has shown that there is sufficient and constantly growing evidence from studies *in vivo* that show the direct genotoxicity of oestradiol 17ß and its catechol metabolites in animal and human tissue as well as the mutagenicity of oestradiol 17ß metabolites in experimental animals:

- Li et al. (2004) have demonstrated that the N7-guanine adduct (N7Gua) and the N3-adenine adduct (N3Ade) of E2-3,4-quinone (the putative carcinogenic E2 metabolite) were present in the DNA of the mammary gland of ACI rats after injection of 4-HO-E2 or E2-3,4-quinone (Exhibit EC – 121).
- Markushin et al. (2003) have detected the N3Ade (and in part N7Gua) adducts of 4-HO-E2 and 4-HO-estrone (E1) in the breast tissue of women (Exhibit EC – 118).
- Chakravarti et al. (2001) demonstrated mutations in the H-ras gene of SENCAR mouse skin after topical application of E2-3,4-quinone, and Chakravarti et al. (2003) found similar mutations in the mammary gland of ACI rats after administration of E2-3,4-quinone. The type of mutations in both *in vivo* animal systems can be explained by depurination of the N3Ade adducts. These experiments are reviewed in Cavalieri et al. (2006) (Exhibit EC – 48).

- Cavalieri et al. (2006) used the Big Blue® rat model to assess the mutagenicity of E2 and 4-HO-E2 *in vivo* and found both compounds to be mutagenic. The mutational spectrum observed for 4-HO-E2 was consistent with the formation and depurination of N3Ade adducts (Exhibit EC – 125)

44. It should be noted that the magnitude of DNA adduct levels and mutagenic activities reported in these studies is not very high and seems to be much lower than encountered with most known genotoxins, which indicates that oestradiol may be a weak genotoxin. This may also be true for the other hormones and this may explain why standard genotoxicity assays show negative or borderline effects with these compounds. Moreover, the genotoxic activity of oestradiol 17β and its metabolites determined in rodent assays *in vivo* may be obscured by the diet, which usually contains high concentrations of phytoestrogens, e.g. from soy. It has been recently reported that several phytoestrogens induce the enzyme quinone reductase, which inactivates the quinones of catechol estrogens and thereby reduces DNA damage (Bianco et al., 2005, Exhibit EC – 124)).

45. The question, therefore, is not that there is no evidence of genotoxicity *in vivo*, but rather how much evidence more is needed by the defending parties before they would be forced to reconsider their views, as did JECFA and Canada recently in relation to other substances, e.g. for Carbadox.

Q14. In your view, does the risk assessment undertaken by the European Communities on oestradiol-17β follow the Codex Guidelines on risk assessment, including the four steps of hazard identification, hazard characterization, exposure assessment, , and risk characterization with respect to oestradiol-17β?

US comment

46. The United States refers to the experts' (Drs. Boobis, Boisseau and Guttenplan) replies to this question in paragraphs 19, 20 and 32 of its submission. In paragraph 19 of its submission, the United States claims that "the experts' responses confirm that, while the EC Opinions engage in hazard identification, the first step of a risk assessment, the Opinion fail to complete any of the remaining three components." The European Communities disagrees with the selective citation and the biased conclusions drawn by the US. Dr. Guttenplan has certainly supported the EC position on this point.

Canada's comment

47. Canada's presentation that "Drs. Boisseau, Boobis and Guttenplan also agree with Canada that the EC failed to follow the Codex guidelines on risk assessments" and that "[t]he experts share Canada's concerns that the EC (and SCVPH) took significant and unjustified short-cuts in the conduct of its risk assessment" is plainly wrong.

48. Neither Dr. Boisseau nor Dr. Boobis or Dr. Guttenplan make any specific comments on Canada's concerns. Thus, to present the experts' replies as if these had said: "Yes, Canada is right" is, to say the least, wishful thinking.

49. More specifically, Dr. Boisseau's position can hardly be described as being "very critical of the EC's decision not to follow the Codex guidelines" as Canada presents it. Dr. Boisseau has explicitly stated that "[T]he European Communities does not indicate anywhere in its submission that it does not intend to follow the Codex guidelines on risk assessment including the four steps of hazard identification, hazard characterization, exposure assessment and risk characterization. On the contrary, the following indicates that the European Communities considers the same approach for assessing the risk associated with the residues of growth promoters." On that basis, how is it possible for Canada to describe Dr. Boisseau's position as "very critical on the EC's decision not to follow Codex guidelines"? Just the opposite is true.

50. While it is true that Dr. Boisseau at the end of his reply has put in brackets a comment whereby "[t]hese two statements call for refining the exposure assessment of hormones residues" it is a complete mischaracterization by Canada to interpret this statement as a criticism that the European Communities should "not abandon the entire risk assessment methodology" and, even more, to take this conclusion as a confirmation of Canada's submission. Again, this is little more than wishful thinking by Canada.

51. It is no surprise that Canada's comment on Dr. Guttenplan's reply is also more than selective. Canada refers to Dr. Guttenplan's alleged criticism on the European Communities' hazard characterization and risk characterization "for the same reasons advanced by others". The European Communities is wondering who are these others and on what basis Canada can make such an unqualified statement.

52. On substance, Canada also completely ignores that Dr. Guttenplan has expressly stated that the "EC has been thorough in following Codex guidelines on hazard characterization and very thorough in exposure assessment." This indeed invalidates directly Canada's own statement whereby the "EC has done very little that resembles an exposure assessment".[5] In this context, the European Communities is also surprised about Canada's description that the European Communities has admitted "that it did not, because it could not conduct an exposure assessment". The paragraph 141 of the EC rebuttal submission quoted by Canada does not support this statement.

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

Q15. Does the identification of oestradiol-17β as a human carcinogen indicate that there are potential adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes? Does your answer depend on whether good veterinary practices are followed? [see paras. 206-207 of EC Rebuttal Submission (US case), para. 121 of EC Rebuttal Submission (Canada case), paras. 97-98 of EC Replies to Panel Questions, para. 76-77, 150 and 155-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission]

US comment

53. The United States refers to the experts' (Dr. Boobis, Boisseau and Guttenplan, Cogliano) replies in paragraphs 34, 38, 42 and 43 of its submission. Conveniently, the United States does not comment on Dr. Boisseau's categorical statement regarding the dependence of his reply on the efficient implementation of good veterinary practices.

Canada's comment

54. From the outset, it should be noted that none of the experts "agree with Canada" on the effect of the carcinogenicity of oestradiol-17β. Indeed, none of the experts take any position on any statement made by Canada.

55. Canada's blunt summary of the experts' replies whereby "most of the experts conclude affirmatively that there would be "no appreciable risk" of adverse effects from exposure from this one minimal source of oestradiol 17β" is inaccurate as the experts differ considerably in their replies and most of them agree with the EC position.

[5] See Canada's comments on expert replies, para. 54.

56. Dr. Boisseau merely says that "oestradiol-17β (…) is not likely to produce adverse effects on human health when it is consumed in meat from cattle treated with hormones for growth promotion purposes". Yet, what is "likely" or not appears to be quite a subjective judgement. Moreover, even Dr. Boisseau explicitly subjects this view to the respect of good veterinary practices as otherwise all the work "to protect human health with regard to veterinary drug residues is meaningless".

57. Dr. Cogliano explicitly states that "the identification of oestradiol-17β as a human carcinogen indicates that there are potential adverse effects on human health when oestradiol-17β is consumed in meat from cattle treated with hormones for growth promotion purposes." This statement hardly supports Canada's theory that the consumption of beef treated with oestradiol-17β does not entail an "appreciable risk".

58. Furthermore, Dr. Guttenplan states that "if potential is taken to mean possible, then an adverse effect cannot be ruled out, but it is unlikely if good veterinary practices are followed". As Dr. Boisseau, Dr. Guttenplan thus refers to the likelihood of adverse human health effect. Yet, as can be seen from his reply (and it is also interesting to contrast this reply with Dr. Boisseau's), such an assessment contains a subjective judgement which justifies that in case of a political decision to take "zero risks" even the slightest minimal chance should be excluded. This is even more justified in this specific case where there are considerable doubts about whether GVP are always respected and which even according to Dr. Boisseau would render all the assumptions "meaningless".

59. Finally, Canada argues that the EC evidence demonstrates that "multiple hormone implants resulted in residues that were still less than the ADIs." However, the data generated by the EC study in question (by *Daxenberger et al. 2000*) documented that the residues after improper use would exceed by far the ADIs.

Q16. Does the scientific evidence relied upon in the SCVPH Opinions support the conclusion that carcinogenic effects of the hormones at issue are related to a mechanism other than hormonal activity? [see para. 148 of the EC Replies to Panel Questions and paras. 35-40 and 46 of US Rebuttal Submission]

US comments

60. The United States refers to the experts' (Drs. Boisseau, Boobis, Guttenplan) replies to this question in paragraphs 34, 36 and 50 of its submission. While pretending that all experts confirm the view that no scientific evidence supports the conclusion that the carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity, the United States has to admit, in the same paragraph (34) that Dr. Guttenplan has taken a much more nuanced view on this issue. The United States' interpretation of other statements made by Dr. Guttenplan, which allegedly suggest, that he links the carcinogenic effects to the hormonal activity, are simply erroneous. The European Communities has explained several times (also above in relation to question 13) that in 2002 there was sufficient evidence from experiments in vivo and this evidence is still growing further. In addition, there is evidence for the mutagenicity of oestradiol-17β as determined in cell culture. For example, Kong et al (Int. J. Oncology, 17: 1141-1149, 2000) reported on the mutagenicity of oestradiol-17β in V79 hamster ovary cells and recently Zhao et al., in a paper whose authorship included Dr. Guttenplan himself (Chem. Res. Toxicol. 19: 475-479, 2006, Exhibit EC-110), reported the mutagenicity of the 4-OH catechol metabolite of oestradiol-17β in BB Rat2 embryonic cells. In this study, multiple treatment of the cells with 50 to 200nM 4-OH oestradiol-17β induced mutations in the BB Rat2 cells in a dose response fashion, with a significant increase being observed after 3 and 3 treatments at the 200nM level. The mutational spectrum resulting from 4-OH oestradiol-17β treatment was different than the "background" mutations seen in the control (untreated) cells further supporting the conclusion that the mutations were in fact caused by the 4-OH catechol estrogen. 2-OH oestradiol-17β did not induce mutations. These results support the difference in carcinogenicity difference

between these 2 catechol metabolites and differences in their ability to cause transformation of normal human breast epithelial cell line MCF-10F as reported by Russo, et al. (J. Steroid Biochem. Mol. Biol. 87: 1-25, 2003, Exhibit EC-115). Furthermore, these results are particularly significant in that the 4-OH catechol metabolite of oestradiol-17β has been detected in the mammary tissue of mice in a model where mammary tumorigenesis is dependent on the presence of estradiol (Devanesan et al. Carcinogenesis, 22: 1573-1576, 2001 (Exhibit EC – 122); Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003, Exhibit EC-90) and in human breast tissue (Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003, Exhibit EC-90).

61. With regard to the study by Chakravarti et al (Oncogene, 20; 7945-7953, 2001, Exhibit EC-48), which is criticised by Dr. Boobis, it should be explained that it detected mutations in the H-*ras* gene in the skin of SENCAR mice following dermal treatment with E2-3,4-quinone, with the specific nature of the mutations detected being consistent with the expected depurination of adenine due to the formation of an E2-3,4-quinone-Adenine adduct. This is relevant to the potential mutagenicity of estradiol in humans because: First, we know that oxidative metabolism of oestradiol-17β to the E2-3-4-quinone metabolite occurs in human breast tissue because E2-quinone adducts to glutathione have been detected (Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003, Exhibit EC-90). Second, adducts of the E2-3,4-quinone with ademine and guanine have been detected in the mammary tissue of ACI rats injected into the mammary gland tissue with 4-OH E2 or E2-3,4-quinone (Carcinogenesis, 25:, 289-297, 2004, Exhibit EC-121). These findings are ignored by Dr. Boobis as well as by the US.

Canada's comment

62. Unlike the US, Canada criticizes Dr. Guttenplan's support for the EC conclusion on the basis that he has not made an analysis on its own. However, Canada has obviously no difficulties in relying on Dr. Boisseau who, in turn is merely invoking (old) JECFA reports and who, therefore, has also not made an analysis on its own. Canada thereby applies a double standard just as it sees fit for its own purposes. In any case, the European Communities has explained above that Dr. Guttenplan has published together with other scientists several papers in peer-reviewed journals, the most relevant one a few months ago (Chem. Res. Toxicol. 19: 475-479, 2006, Exhibit EC-110) which has used the Big Blue® rat model to assess the mutagenicity of oestradiol-17β and 4-HO-E2 *in vivo* and found both compounds to be mutagenic. The mutational spectrum observed for 4-HO-E2 was consistent with the formation and depurination of N3Ade adducts.

Q17. Could you comment on Canada's statement that "the studies commissioned by the European Communities also failed to find evidence of "catechol metabolites" – that is the oestradiol metabolites identified as the source of the genotoxic potential – in meat from treated animals"? What would be the implication of an absence or presence of catechol metabolites? [see para. 102 of Canada Rebuttal submission, EC Exhibit 51A]

US comment

63. The United States refers to Drs. Boisseau's, Boobis' and Cogliano's replies to this question in paragraph 44 of its submission and very conveniently omits any reference to Dr. Guttenplan's straightforward reply.

64. Furthermore, its reference to Dr. Cogliano's reply is misleading as Dr. Cogliano does not conclude "that detectable levels of catechol metabolites were not formed from the parent compound", but rather concludes that "*the absence of catechol metabolites could imply either* (1) [the above] *or* (2) that some level of catechol metabolites was formed that the test methods were not sufficiently sensitive to detect it." (emphasis added) Indeed, as the EC has explained above (in relation to question no 13), there is sufficient and constantly growing evidence from studies *in vivo* that show the direct

genotoxicity of oestradiol 17ß and its catechol metabolites in animal and human tissue as well as the mutagenicity of oestradiol 17ß metabolites in experimental animals.

65. It should be noted that the magnitude of DNA adduct levels and mutagenic activities reported in these studies may not be very high. It seems indeed to be much lower than encountered with most known genotoxins, which indicates that oestradiol may be a weak genotoxin. However, this can also be true for the other hormones and this may explain why standard genotoxicity assays show negative or borderline effects with these compounds. Moreover, the genotoxic activity of oestradiol 17β and its metabolites determined in rodent assays *in vivo* may be obscured by the diet (Bianco et al., 2005, Exhibit EC-124).

66. Finally, that oestrogen may be genotoxic by direct or indirect mechanisms of action is now admitted even by the US since its 2002 Carcinogenesis Report, cited above, and any argument now to the contrary by the US is necessarily not credible.

Canada's comment

67. Canada takes issue with Dr. Guttenplan on the amounts of catechol metabolites by referring to "other experts'" confirmation. However, since Canada does not identify these other experts this is a rather unqualified remark. On substance, the European Communities finds it remarkable that Canada does not criticize Dr. Guttenplan's statement that even "the lack of catechols in meat does not imply that meat from estrogen-treated cattle is without risk for genotoxicity".

68. Moreover, the European Communities would emphasize that, in the absence to the contrary, Canada obviously agrees with Dr. Cogliano's statement whereby "the presence of catechol metabolites would support the potential for adverse effects to occur. The absence of catechol metabolites could imply either (1) that detectable levels of catechol metabolites were not formed from the parent compound or (2) that some level of catechol metabolites was formed that the test methods were not sufficiently sensitive to detect it." This is the most likely explanation, as stated above.

Q18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol-17β is genotoxic. Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see paras. 118-119 of EC Rebuttal Submission (US case), paras. 123-124 of EC Rebuttal Submission (Canada case), paras. 87-91 and 153-156 of US First Submission, paras. 35-40 and 46 of US Rebuttal Submission, and paras. 90-97 of Canada Rebuttal Submission]

US comment

69. The United States refers to Drs. Boobis' and Cogliano's replies to this question in paragraphs 35 and 44 of its submission and very conveniently omits to refer to Drs. Boisseau's and Guttenplan's replies. The latter's reply certainly does not "confirm" - as the United States claims (at paragraph 35) – "that the scientific evidence cited by the EC in its Opinions does not support the conclusion that estradiol 17β is genotoxic at levels found in residues in meat from cattle treated with growth promoting hormones." Quite to the contrary, Dr. Guttenplan confirms the existence of such evidence and states that "the evidence now is much stronger" citing a study of 2004.

70. Moreover, the US argues (at para. 36) that the European Communities has failed to explain why its evaluation of estradiol 17β was not subject to a CVMP guideline requiring confirmation of an in vitro positive using an appropriate *in vivo* assay. This comment is disingenuous because the pharmaceutical industry, the defending members and JECFA, i.e. those arguing that these substances are safe, should produce the evidence showing that estradiol 17β is not genotoxic *in vivo*. The EC has fulfilled its obligations by funding a number of studies and also by collecting the growing evidence

from experiments *in vivo* showing the direct genotoxicity of these hormones, in particular of estradiol 17β. It is now high time that the US (and Canada) stops criticising the European Communities for absence of evidence which itself did not have when it approved these hormones more that 30 years ago and makes an effort to prove what it preaches, that is that these hormones are not genotoxic by direct action. Instead of criticising the European Communities on the basis of purely hypothetical assumptions, the US should have tried to explain the statement from its 2002 Carcinogenesis Report which states:

> "The evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor. *In addition, there is evidence that other mechanisms may play a role in the carcinogenic effects of estrogens in some tissues.* Prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. *Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects.* The relative importance of each mechanism is likely a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state (Yager and Liehr 1996)." (emphasis added)

Canada's comment

71. Canada's interpretation of Dr. Boisseau reply is quite astonishing. First, Canada tries to construe from Dr. Boisseau's reply a difference for a substance having "genotoxic potential" and being "genotoxic". Yet, nowhere in his reply does Dr. Boisseau address this issue so that Canada can hardly take this response as support for its own theory. Moreover, Canada describes Dr. Boisseau's reply on the establishment of an ADI by JECFA in 1999 as "pointing to the need to place exposure to oestradiol 17β from this source into context." It will remain Canada's secret what it means by such a description, since Dr. Boisseau instead submitted that the ADI was established "in order to present in a more convincing way the outcome of its [JECFA's] assessment".

72. In respect of Dr. Boisseau's reply it is also difficult to see how Canada can claim support for its assumption that oestradiol 17β is not genotoxic *in vivo*. He does not say so in his reply to Question 18 and even Dr. Boisseau's reply to Question 13 does not contain such a general statement.

73. The comments by Canada (at paras. 72-73) are subject to the same criticism mentioned above for the statements made by the US. Indeed, the UK VPC constitutes quite a remarkable evolution on this point from its previous evaluation of these hormones in 1995, and it is certainly less categorical in its findings (it uses the terms "is likely") than Canada. Even so, however, the statement quoted by Canada (at para. 72) contrasts sharply with the findings in the 2002 US Carcinogenesis Report quoted above by the European Communities, which Canada has chosen to ignore.

Q19. The European Communities states that "... it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol-17β) a threshold can not be identified. Therefore it cannot be said that there exist a safe level below which intakes from residue should be considered to be safe. Therefore the fact that doses used in growth promotion are low is not of relevance". Does the scientific evidence referred to by the European Communities support these conclusions? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 201 of EC Rebuttal Submission (US case), paras. 120-122 of EC Rebuttal Submission (Canada case), paras. 73 and 86-98 of Canada Rebuttal Submission, paras. 87-91 and 153-156 of US First Submission and paras. 35-40 and 46 of US Rebuttal Submission]

US comment

74. The United States refers to the experts' (Drs. Boobis, Boisseau, Cogliano, Guttenplan) replies to this question in paragraphs 37 through 40 of its submission. Its reading of Dr. Guttenplan's and Dr. Cogliano's replies is erroneous. On Dr. Guttenplan, the United States claims that he does not take a clear view on whether oestradiol 17β is genotoxic at level found in residues in meat from cattle treated with growth promoting hormones. However, this is not what Dr. Guttenplan has said.

75. On Dr. Cogliano, the United States' claims that he "concurs [with Dr. Boobis] "noting that the EC's statement regarding the lack of a threshold has not been demonstrated by the scientific evidence." Quite to the contrary, however, Dr. Cogliano said: "The EC's statement that a threshold cannot be identified reflects their view of genotoxic mechanisms, just as the contrary statement that there is a threshold and that this threshold is above the levels found in meat residues reflects how Canada and the US view genotoxic mechanisms. Neither statement has been demonstrated by the scientific evidence, rather, they are different assumptions that each party uses in their interpretation of the available evidence."

Canada's comment

76. Canada's statement that Dr. Boobis' and Dr. Cogliano's replies would support its own argument that for substances endogenously produced by human body there must be threshold is, at least, a challengeable conclusion. Indeed, neither Dr. Boobis nor Dr. Cogliano, who apart from this question obviously have a different perception about the genotoxicity of these hormones, do at all address this argument. Canada makes (at para. 74) the rhetoric argument that "humanity would have been wiped out by cancer millennia ago". This statement is highly unscientific. First, humanity did not use to eat meat treated with hormones, save for approximately the last 30 years and this only in the US (and a bit later in Canada). Secondly, the rates of cancer in general (including prostate and breast) are increasing, in particular in the US, where they are higher by about 20% compared to those in Europe. Third, as the European Communities has explained above, it may be that these hormones are weak carcinogens, which explains why they could not be detected by the old and most of the existing assays. But the rates of cancer observed today are a serious cause for concern. Furthermore, the implication of the Canadian claim that a substance that is produced endogenously cannot be carcinogenic when administered exogenously is incomprehensible.

77. The same applies for Canada's claim (at para. 75 and 76) that even EFSA has recognised safe thresholds for genotoxic substances. This is simply not true because the EFSA opinion cited by Canada, although issued for another purpose, simply states that the incidence of cancer may not be increased, but it does not state that there is no risk from such substances.

78. Canada states (at para. 74) "that experts from around the world" contradict the EC' claim, but it manages to cite only the UK VPC and the JECFA reports. These are the "experts around the world". Canada fails however to cite the well known reports from the IARC – which as its name indicates is the best placed international institution on issues of cancer research and prevention – nor does Canada pay any attention to the US Carcinogenesis Report.

79. It is clear from the replies of the experts that they are divided on this issue (2 against 2), but if the expected replies of the other 2 experts are added, then the majority of the experts agrees in substance with the EC position.

Q20. In your view, how do the European Communities' conclusions above relate to the conclusion by Codex that "establishing an ADI or MRL for a hormone that is produced endogenously in variable levels in human beings was considered unnecessary"? To what extent,

in your view, has JECFA's conclusion that oestradiol "has genotoxic potential" affected its recommendations on this hormone?

US comment

80. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) and JECFA's (to a related question)[6] replies to this question in paragraph 41 of its submission. The European Communities disagrees with the summary of the statements made by the US in that paragraph. That oestradiol 17β is carcinogenic by both direct and receptor mediated mechanisms is no longer in doubt (see the latest article by Cavalieri et al., 2006, see Exhibit EC-125). This has been stated also by the US since its 2002 Carcinogenesis Report to which the US fails to refer.

Canada's comment

81. Canada draws an unjustified conclusion from the experts' replies whereby "Drs. Boisseau, Boobis and Guttenplan all consider the EC's conclusion about the absence of thresholds to be inconsistent with the Codex standards." Yet, the answers of these experts are much more nuanced than Canada presents. For instance, Dr. Boisseau only states that the "European Communities' conclusions are questionable". It goes without saying that there exists a difference between "inconsistent" (as Canada qualifies it) and "questionable". The same applies to Dr. Boobis who submits that the "EC conclusion on the absence of safety at any level of exposure is somewhat at odds with the underlying basis of the Codex conclusion regarding the need for an ADI or MRL". Again, if something is "somewhat at odds" it does not mean that it is "inconsistent". Finally, Dr. Guttenplan merely states that the European Communities' conclusions above are "at variance" with those of Codex. It is difficult to see how this can be reconciled with Canada's statement that the EC's conclusions are "inconsistent" with Codex standard.

82. In this context, it is also an unqualified assumption by Canada that "to the extent that most of the experts found the EC conclusions on the matter are unsupported by the evidence and are "questionable", they support the existing Codex standards." Indeed, the mere comparison between a Codex standard and a respective EC conclusion does not lend any support whatsoever about the value of this standard.

83. Finally, the European Communities would take issue with Canada's unsupported conclusion that the "experts' answers also confirm that even though JECFA acknowledged that oestradiol 17β has "genotoxic potential", this acknowledgment did not generate concern about the safety of the substances and therefore did not affect its recommendation". Indeed, none of the experts makes any qualified statement to this effect and Canada's inference from the experts' replies is therefore completely baseless. At most, Dr. Boobis stated that "I do not believe that JECFA's conclusion that oestradiol has "genotoxic potential" affected its recommendations on this hormone (…)". As can easily be seen this is a mere unsubstantiated guess and personal opinion by one expert whereas the other experts remain mute on this issue. Thus, Canada's presentation is far from being an objective description of the facts.

84. What is even more important is that the statements by Dr. Boisseau and Dr. Boobis are partial because they do not consider the totality of the available evidence, such as that mentioned by the European Communities and in particular the reports from the IARC and the US Carcinogenesis Report which have been made available to them. Dr. Boobis concentrates only on the JECFA reports, which are based on very old data.

[6] Question 20 of the questions asked to Codex, JECFA and IARC is about …

Q21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol-17β, when consumed as residues in meat have genotoxic potential? Does your answer depend on whether good veterinary practices are followed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see, *inter alia*, the SCVPH Opinions and paras. 63, 83, 89-91 and 93 of US First Submission, paras. 131-136 of Canada Rebuttal Submission]

US comment

85. The United States refers to the experts' (Drs. Boobis, Guttenplan and Boisseau) replies to this question in paragraph 50 of its submission. Overall, the experts' replies are much more nuanced than what the United States suggests when claiming that they all "confirm that the scientific materials cited by the EC in its Opinions do not demonstrate or support the conclusion that any of the five hormones has genotoxic potential or is carcinogenic by a mechanism other than hormonal activity." As both Dr. Boobis and Dr. Guttenplan report, there are some data that indicate the possibility of genotoxic effects. The data are probably not "conclusive" (Dr. Guttenplan) and perhaps not "convincing" (Dr. Boobis) to everyone, but it is more than a sufficient and legitimate basis for a legislator acting on the basis of precaution to adopt provisional measures.

Canada's comment

86. Canada's blunt statement that "Drs. Boisseau, Boobis and Guttenplan all refute the EC's claims about the potential genotoxicity of the other five hormones" is not supported by the experts' replies. For instance, Dr. Boobis merely states that "there is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic". However, what is "convincing evidence"? In the same vein, Dr. Guttenplan refers to "no conclusive evidence" or "some evidence that certain of the hormones have genotoxic potential". Yet, what is "conclusive" or what means "some evidence"? Whatever it means, it can in any case not justify Canada's unqualified conclusion that there is no "potential genotoxicity of the other five hormones". Rather, their statements confirm the EC position that there are considerable gaps and uncertainties in our knowledge, which justify applying Article 5.7 of the *SPS Agreement* in order to achieve ones chosen level of health protection.

Q22. How would you define *in vivo* DNA repair mechanisms? How effective or relevant are *in vivo* DNA repair mechanisms with respect to potential genotoxic effects from residues of the growth promoting hormones at issue when consumed in meat? Does your answer depend on whether good veterinary practices are followed in the administration of these hormones? To what extent does the scientific material referred to by the European Communities take into account these mechanisms in its evaluation of potential occurrence of adverse effects from residues of growth promoting hormones? Would your reply have been different at the time of adoption of the Directive in September 2003 and if so, why? [see paras. 40 and 46 of US Rebuttal Submission, footnote 107 of US First Submission, and para. 89 of Canada Rebuttal Submission]

US comment

87. The United States refers to the experts' (Drs. Boobis, Guttenplan) replies in paragraph 31 of its submission. The US again misrepresents the views of the scientists, in particular those of Dr. Guttenplan, who stated *inter alia* that "a small fraction of damage inevitably escapes repair" and that consideration of this issue by the SCVPH is in fact irrelevant to the debate (even though he found some references in the SCVPH assessment that discussed this issue).

Canada's comment

88. Canada spends again a number of paragraphs (at paras. 85-89) trying to interpret the experts' replies as supporting its views on this question. But as Dr. Guttenplan has explained in his reply, there is no reason to believe that the repair mechanism in the case of these hormones would be different from what is happening in other instances. It is also inevitable that some DNA damage will remain unrepaired, as is the case with so many other direct genotoxic substances. As the 2002 US Carcinogenesis Report states: *"... prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression…[and that]…the relative importance of each mechanism is likely to be a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state"*. This means that to go down the road advocated by the defending parties and Dr. Boobis, i.e. in trying to estimate how much of the DNA damage is likely to be repaired in time and what would be the carcinogenic potential of the damage left unrepaired would not be possible in view of so many specificities involved, supposing one could undertake this kind of estimation in a reliable way. That is why Dr. Guttenplan states that this issue is irrelevant for the debate on the genotoxicity of oestradiol and whether an ADI for such substances could or should be fixed.

Q23. To what extent is it necessary or possible to take into account the "long latency period" of cancer in the conduct of a risk assessment, which is supposed to assess carcinogenic effects of these hormones when consumed in meat? Have the hormones in dispute been used as growth promoters over a sufficient number of years for an assessment of their long-term effects on human health to be made? [see para. 149 of EC Rebuttal Submission (US Case), para. 143 of EC Rebuttal Submission (Canada case)].

US comment

89. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) replies on this question in paragraphs 57 and 58 of its submission.

90. In Footnote 127 the United States is suggesting that there is no evidence of adverse effects after more than 20 years of consumption of beef from cattle treated for growth promotion purposes. However, as Dr. Boobis rightly concludes "... a negative result from such an observational study would not resolve the issue."

91. Furthermore, the United States misinterprets Dr. Guttenplan's statement that "hormones in meat [...] have now been consumed for a sufficient number of years to observe strong or moderate increases in risk." The United States pretends that Dr. Guttenplan hereby suggest that there is no such evidence. However, the European Communities does not interpret in the same way Dr. Guttenplan's statement, quite the opposite.

Canada's comment

92. Canada summarises the replies of the scientists in a partial way in paragraphs 90-93 to come to the conclusion that "… exposure to residues of hormones in meat from treated animals is only a small fraction of the overall exposure to the substance from a variety of sources, including that produced endogenously within the human body ...". A careful reading of the replies of the scientists however does not support this conclusion. Indeed, none of the scientists explicitly said that the exposure is only "a small fraction", because it is not easy to estimate the level of the residues. For instance, the 2002 US Carcinogenesis Report simply stated that the use of these hormones for growth promotion increases the level of residues to above "their normal levels". The point therefore is that the two scientists cited by Canada have not and could not have come to the conclusion that the residues is

a small fraction, not least because they do not know it and could not prove it (because of the background and other confounding factors).

Q24. To what extent is it possible to identify possible co-founding factors causing cancer and attribute them to identified sources? What are the implications of these factors for the conduct of a risk assessment evaluating the adverse affects caused by residues of growth promoting hormones in meat? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

US and Canada's comments

93. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) replies on this question in paragraph 59 of its submission and Canada in paragraphs 94-96. They both appear to accept (as do all the scientists) that there is now an association established between meat consumption and cancer, but they dispute that the evidence is there to clearly establish a causal link between the residues in meat from hormone-treated cattle and the high cancer incidence. But the European Communities has not argued it and does not take issue with the fact that it is difficult to establish that causal link. What is very important to note, however, is that the defending parties cannot make the argument that because the establishment of the causal link is difficult, there should be assumed that such a risk is insignificant or does not exist because the added burden is thought to be small. Furthermore, the defending parties can no longer make their simplistic argument that humans are exposed to hormonal residues from so many other sources, so a small additional exposure from the residues in treated meat would not make any difference. This simplistic argument has been made over and over again by the defending parties to the Panel and it is now clear that there is no scientific basis to this claim because they cannot establish the causal link of what they argue. However, the evidence is there, and it is indeed growing, associating high rates of cancer with meat consumption, and these rates of cancer are higher in the US than in Europe, and one day if the US and Canada would like to find out more about any possible causal link between the two so as to protect their people the same way as the European Communities does, it could undertake the studies which Drs. Cogliano and Guttenplan have suggested.

Q25. To what extent do the three recent studies referred to by the European Communities confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones? Please also comment on the EC statement that one of the studies "was carried out after the introduction of the ban on the use of hormones for growth promotion in Europe, which means that the subjects should have been exposed to hormone-free meat in their diet. This may further imply that it cannot be excluded that the risk of cancer may be further increased if meat treated with hormones for animal growth promotion were to be consumed". [see paras. 145-148 of EC Rebuttal Submission (US case) and paras. 139-142 of EC Rebuttal Submission (Canada case), footnote 97 in para. 147 of EC Rebuttal Submission (US case), and Exhibits EC-71, 72, 73]

US and Canada's comments

94. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan and Cogliano) replies on this question in paragraphs 61 through 63 of its submission. Contrary to what the United States suggests, the experts are far from "[agreeing] that the three studies demonstrate no such risk." While Dr. Boobis holds this view, both Dr. Cogliano and Dr. Guttenplan, on the contrary, confirm that these studies indicate or suggest risks. Indeed, as the European Communities has explained above, at least 2 out of the 4 scientists seem to agree that this kind of epidemiological evidence could provide indirect information indicating that there may be a causal link.

95. It is therefore surprising the Canadian comment (in para. 102) that the European Communities is "manipulating a genuine scientific interest". This kind of manipulating tactic has been deployed by the defending parties since 1997, in their argument that the risk from residues in treated meat with these hormones is miniscule compared to the higher exposure of humans to intake from other natural foods (meat, broccoli, soya, eggs, etc.), a statement which the Appellate Body has dismissed as "an absurdity" in its 1998 *Hormones* report (at para. 221). Conversely, the EC argument has been supported by at least one panel expert in the 1998 *Hormones* case and appears to be considered relevant by two of the present experts. Indeed, it is recalled that during the 1997 panel report on *Hormones*, one of the experts for the Panel (Dr. G. Lucier) had then stated:

> *"For every million women alive in the United States, Canada, Europe today, about a 110,000 of those women will get breast cancer. This is obviously a tremendous public health issue. Of those 110,000 women get breast cancer, maybe several thousand of them are related to the total intake of exogenous oestrogens from every source, including eggs, meat, phyto-oestrogens, fungal oestrogens, the whole body burden of exogenous oestrogens. And by my estimates one of those 110,000 would come from eating meat containing oestrogens as a growth promoter, if used as prescribed."*

96. However, the Appellate Body in 1998 denied evidentiary value to Dr. Lucier's statement for the reason that his opinion "… does not purport to be the result of scientific studies carried out by him or under his supervision focusing specifically on residues of hormones in meat from cattle fattened with such hormones …". (at para. 198 of the 1998 Appellate Body report).

Q26. Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see pages 17-19 of 1999 Opinion of the SCVPH and related Tables A4-A5 on pages 83-91]

US comment

97. The United States refers to the experts' (Drs. Boobis, Boisseau, Guttenplan, Cogliano) replies on this question in paragraphs 59, 60 and 63 of its submission. The United States' bold assertion that "the experts' responses confirm that the epidemiological studies cited by the EC in its Opinion fail to identify a link between hormone residues in meat and cancer" is once again a misrepresentation of what these experts actually stated. To take the example of Dr. Boobis, while he does state 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 human," he qualifies that statement in the very next sentence pointing to the existence of "some studies that are consistent with such an association …" (studies which admittedly he thinks have other possible explanations, some of which are more plausible than hormones in meat being causal). In the same vain, Dr. Guttenplan also concedes that "the results are at least consistent with a possible effect of hormones on breast and prostate cancer."

Canada's comment

98. Canada submits that the breast and prostate cancer rates between Europe and North America are "relatively similar". However, on the basis of the figures mentioned by Dr. Boobis the difference would still be around 20% higher in the United States, which can hardly be described as "relatively

similar". In this context, it is also amazing how Dr. Boobis minimizes the potential hormones treated beef on these differences by linking any difference rather to higher meat consumption. Apart from the fact that Dr. Boobis is just engaging in some "best guessing effort", it is undeniable that the higher meat consumption is intrinsically linked to higher hormones consumption. Thus, it defies any logic and common sense, as Dr. Boobis does, to refer to one single figure on consumption but leaving aside the very fact that the higher consumption inevitably entails a higher intake of hormones.

(b) Residue analysis

Q27. How do the residues in meat from cattle treated with the three synthetic growth promoting hormones differ from residues in meat from cattle treated with the three natural growth promoting hormones at issue?

US and Canada's comments

99. The United States and Canada do not refer to or comment on the experts' (Drs. Boisseau, De Brabander) replies to this question.

Q28. How do the hormones naturally present in animals, meat, or human beings differ from the residues in meat of the three natural hormones used for growth promotion purposes?

US comment

100. The United States does not refer to or comment on the experts' (Drs. Boisseau, De Brabander) replies to this question.

Canada's comment

101. Contrary to Canada's view, Dr. De Brabander's opinion is not "much less clear". Rather, Dr. Brabander is very explicit and detailed in his reply suggesting that the residues in meat of the three natural hormones used for growth promotion purposes are not identical to the hormones naturally present in animals. What is even more questionable is that Canada criticises Dr. De Brabander's statement on the ground that "his position would be inconsistent with the detailed residue evidence reviewed by JECFA in its 1999 residue monograph. The monograph presents detailed data on hormone concentrations in various tissues, including muscle and fat, in untreated heifers and steers. Dr. De Brabander's suggestion in this regard simply does not withstand close scrutiny." Yet, as we know and as JECFA and Codex admitted openly in their replies – including that by Dr. Boisseau – the residue data used by JECFA in 1999 are essentially the same as those used in 1988 and that for the most part they date back to the 1960s and 1970s, whereas those used by Dr. De Brabander are the most recent ones. Therefore, the Canadian claim cannot be taken seriously. The European Communities reiterates once more its claim to the defending parties to provide their residues data and the Panel to request those data from JECFA and make them available to the experts, so that close scrutiny could indeed be exercised.

Q29. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the synthetic hormones found in meat in their assessment of the risks from such residues? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? How do they compare with the MRLs set by Codex? [see paras. 165-176 of EC Rebuttal Submission (US case); pages 55-68 of the Opinion of the SCVPH of 30 April 1999 in US Exhibit 4, para. 144 of US First Submission, Exhibits US-6 and 7, footnote 46 of US Rebuttal Submission]

US and Canada's comments

102. The United States refers to the experts' (Drs. Boisseau, De Brabander) replies to this question in paragraphs 90, 91 to 93 of its submission. The US criticises Dr. De Brabander's reply as not being based on concrete evidence. The US further cites Dr. Boisseau as stating that "…older data is neither irrelevant or "bad" data simply due to its age. Rather, it is the quality and quantity of data that is important, and for the hormones at issue, a great deal of high quality data exists." As a general statement, the European Communities surely agrees with it. However, as regards the data on MGA used by JECFA date from the 1960s and 1980s, they are industry studies not published in any peer-reviewed journal, and have not been seen by anyone else except the US and JECFA (see Exhibit EC-127). Moreover, as long as these parties refuse to make them available for verification, it is legitimate for an expert and the European Communities to question their scientific quality and credibility, given that the more recent data produced by the EC studies and those available in open literature do not support the conclusions which the defending parties and JECFA pretend to draw from those old data.

103. For these reasons, it is very inaccurate and misleading the comment made by Canada (at para. 111) that the methods used by JECFA are "modern" and validated ones. The problem is not only whether they are modern and validated but whether the residues which they are supposed to measure, if the MRLs were to be adopted one day by Codex Alimentarius, are taken with these modern methods or in the 1960s and 1980s when these so-called "modern" methods did not even exist. This is the point. Indeed, Canada (and the US) unjustifiably and incorrectly criticise the reply by Dr. De Brabander because he made his point as follows: "*At the time they are [the residues] produced (1987) there were no analytical methods available to quantify these residues at that concentration level in a correct way (methods as GC-MS-MS or LC-MS-MS)"*. It is obvious, therefore, that Canada's comment (at para. 111) that "…his cursory conclusion is in stark contrast to the extensive evaluation of residue data conducted by JECFA. In particular, recent residue data from studies using "modern" validated methods (HPLC-MS, GC-MS and LC-MS) were assessed in the JECFA Residue Monograph for the 58th Meeting. All ten studies cited date from 1999 to 2002" is inaccurate because: First, JECFA in 2000 did not carry out any extensive evaluation of the data, it simply took for granted the old and unpublished data of the pharmaceutical industry; second, the ten studies cited in the 58th meeting of JECFA are those that will be used if the MRLs for MGA proposed by JECFA will be accepted one day in the future by the Codex Commission, but they are clearly not those used to generate the data in the 1960s and 1970s.

104. Moreover, Canada's summary of Dr. Boisseau's reply is misleading. Dr. Boisseau not merely stated that the SCVPH did not conduct a quantitative assessment but rather states more accurately that "[a]s, in its 1999 report, SCVPH concluded "that no threshold level and, therefore, no ADI can be established for any of the six hormones" (including the three synthetic ones), *there was no need for SCVPH* to conduct a quantitative assessment (…)." (Emphasis added). Obviously, it makes a difference if the SCVPH, as Canada insinuates, failed to do a quantitative assessment or, as Dr. Boisseau states there was a very good reason for SCVPH not to do such an assessment.

Q30. To what extent do the SCVPH Opinions evaluate evidence on the actual residue levels of the three natural hormones in meat in their assessment of the risks from such residues? Is it possible to compare these to the ADIs recommended by JECFA in 1999? Are specific references provided as to how the evidence on residues relates to the observance of good veterinary practices or lack thereof? [see paras. 120-123 and 155-164 of EC Rebuttal Submission (US case), pages 33-54 of 1999 Opinion in Exhibit US-4, para. 144 of US First Submission, and 52nd JECFA Report in Exhibit US-5]

US and Canada's comments

105. The United States refers to Dr. Boobis' reply to this question in paragraph 90 of its submission. No reference is made to Dr. De Brabander's reply. As the European Communities has noted in its comments of 30 June 2006 on Dr. Boobis' reply to this question, his position is incorrect because the SCVPH did perform the comparison of the ADI and MRL values proposed by JECFA with those generated by the EC studies that were reviewed by the SCVPH. In addition, the reply of Dr. De Brabander confirms the EC finding that the data used by JECFA are old and their validity can be questioned, until we are given the means to see and review them. The comment by the US (in para. 90) on the reply of Dr. Boobis is misleading, because it seems that both have not understood that JECFA reviewed old data that did not take into account realistic conditions of use of these hormones, unlike the data generated by the EC studies for the first time and examined by the SCVPH. Dr. Boobis asks the rhetorical question that "the frequency of occurrence of such misuse" is not stated. However, the studies cited at Exhibits EC-65, 67, 68, 69, 70 and 70-73 show that the higher the frequency the higher the risk will be. But in the case of prepubertal children the EC studies have clarified explicitly that even a unique occurrence or an occasional one would be sufficient to lead to residue levels in meat that would exceed by many times their endogenous production of these hormones.

106. Since Dr. Boisseau referred back in his answer to this Question to his reply to Question 29, the same criticism on Canada's summary of Dr. Boisseau's statement applies here.

Q31. Please comment on the US statement that "concentrations of oestradiol-17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, i.e., residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of oestradiol-17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." In your reply please take into account the US 11th Carcinogenesis Report where it is stated that "Meat and milk may contain estrogens. Veterinary use of steroidal estrogens (to promote growth and treat illness) can increase estrogens in tissues of food-producing animals to above their normal levels" and the statement by the European Communities that "meat consumption from pregnant heifers is exceptional as usually these animals are not slaughtered. [see paras. 51 and 144 of US First Submission and Exhibits US-6 and 7, para. 98 of EC Replies to Panel Questions, Exhibit EC-101, and para. 2.3.2.3 of the 1999 Report of SCVPH]

US comment

107. The United States refers to Dr. De Brabander's reply to this question in paragraph 96 of its submission. No reference is made to Dr. Boisseau's reply. The United States comments on the view taken by Dr. De Brabander that "there is no need to add more [hormonal substances] by artificial ways" stating that this is Dr. De Brabander's "personal opinion or policy statement." As a matter of fact, Dr. Boisseau seems to take the opposite view by referring to a "theoretical" of "no additional intake of residues [being] acceptable." What both experts express here, is indeed a policy statement, a policy statement of the kind the European Communities as a risk regulator has every legitimacy to make.

Canada's comment

108. In its comments to the experts' replies, Canada again demonstrates its very selective perception of what the experts actually said. While it quotes *in extenso* Dr. Boisseau (who may be understood to support Canada's position) it basically ignores Dr. De Brabander's very critical remarks regarding the significant increase of estradiol-17β in human food if all animals were treated

accordingly. The Panel would be well advised to take good note of Dr. De Brabander's response and to draw its own conclusions why Canada is unwilling or unable to comment on the serious questions in relation to animal welfare, environment and consumer protection as raised by Dr. De Brabander.

109. More importantly, however, Canada resorts (in paras. 116-117) to its dear and old argument (in the absence of anything else) that "…in order appropriately to understand the risks associated with the use of growth-promoting hormones, one must view the exposure to these hormones in their overall context, including the wide exposure to natural hormones from other dietary sources and endogenous production of natural hormones." However, this kind of argument has been clearly rejected by the Appellate Body in the 1998 *Hormones* case as "an absurdity". Moreover, the Appellate Body has also found that the occasional use of meat from pregnant cows or those treated for therapeutical or zootechnical purposes does not lead to arbitrary or unjustifiable discrimination and do cannot undermine the EC's level of health protection (at paras. 222-225 of its report).

Q32. Please comment on the conclusions of the EC risk assessment (Opinion of the SCVPH of April 2002) that ultra sensitive methods to detect residues of hormones in animal tissues have become available but need further validation. What is the significance of this with regard to identifying whether the natural hormones in meat are endogenously produced or are residues of hormones used for growth promotion purposes?

US and Canada's comments

110. The United States refers to Dr. Boisseau's reply to this question in paragraph 93 of its submission. No reference is made to Dr. De Brabander's reply. However, Dr. De Brabander states that "there are now new data available demonstrating that the pattern change of hormones by the application of the 'natural' hormones used for growth promotion purposes." This is in direct contradiction with Dr. Boisseau's statement that ultrasensitive detection methods would be "less useful in the case of the three natural hormones, which are endogenously produced by food producing animals." The United States seems to agree with Dr. Boisseau's comment without, however, commenting clearly on this contradiction. The basic point Dr. De Brabander was making in his reply is that the residue examined by JECFA were generated with the old methods and that new methods should be used now to re-evaluate them. This is in agreement with the position of the European Communities. Dr. Boisseau's reply is besides the point, because the new powerful and ultra sensitive methods will always be required in order to determine the origin of residues in meat, for example in order to determine whether is it endogenous or exogenously administered and whether there was an abuse or misuse.

Q33. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by the Codex Committee on Residues of Veterinary Drugs in Food? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

US comment

111. The United States refers to the experts' (Drs. Boisseau, Boobis, De Brabander) replies to this question in paragraphs 97 through 99 of its submission and also to Codex' and JECFA's replies on

related questions.[7] Contrary to what the United States pretends there is complete dissent among the experts on the reasons why JECFA re-evaluated the three natural hormones,[8] and the Panel is referred here to the reply of JECFA which admits that the ADIs were set because of the new evidence that became available in the meantime.

Canada's comment

112. It is not clear whether Canada's comment is fully consistent with its comment on Question 18. In this question Canada assumes that the "genotoxic carcinogen [of oestradiol] appears to have promoted at least in part JECFA's 1999 re-evaluation", whereas in its comment to Question 18 Canada denied that JECFA's establishment of an ADI was related to its finding about "potential genotoxicity", (see para. 71 last sentence).

113. Moreover, what is interesting is that Dr. Boobis appears to recognise that "in the intervening time from the first to the second evaluation, it became clear that exposure to the natural hormones, albeit at levels appreciable higher than found in meat from treated cattle, could have adverse effects in humans". This is remarkable, as he admits that there is a problem of principle (despite all the talk about eggs, milk and broccoli etc.), and it appears to be rather a question of "how much" is acceptable (see also Canada's comment in this respect at para. 125, last sentence).

114. Canada's comment (at paras. 127-128) apparently approving the explanations provided by JECFA and Dr. Boobis is inadequate. Indeed, after the CCRVDF refused to consider the 1999 re-evaluation of the three natural hormones, where ADIs were considered necessary in order to avoid the risk of cancer identified, the continued 1988 indication that MRLs are not "necessary" do not enable the countries using these hormones to see if the ADIs are reached or exceeded. It would therefore be imperative that JECFA and Codex review again all these hormones soon by taking into account all the latest evidence and data available, in particular, those generated by the studies sponsored by the European Communities.

Q34. Please comment on the EC argument that the 1999 JECFA report based its findings on (a) outdated residues data and (b) not on evidence from residues in meat but on studies with experimental animals and on general studies of IARC. If the data were not new, did JECFA take this into account in its evaluation? What are the implications of using such data for the purpose of conducting a risk assessment? How reliable are extrapolations from animal studies to possible adverse effects on humans? How does this compare with the kind of data and studies used with respect to other veterinary drugs? [see para. 120 of EC Rebuttal Submission (US case), para. 102 of EC Rebuttal (Canada case)]

US comment

115. The United States refers to Dr. Boisseau's reply to this question in paragraphs 49, 92 and 111 of its submission. No reference is made to Dr. De Brabander's reply. The reference to Dr. Boisseau is always the same namely his statement that "the quality and the number of the available data are more important than the dates at which these data have been produced." The European Communities has already commented on this statement, which it considers scientifically unsound (see EC comments on replies to question 34).

[7] Question 20 in questions asked to Codex, JECFA and IARC.

[8] Of course, there is agreement on the outcome of that evaluation, but that is not the question that was put to the experts. The outcome – JECFA finding that these hormones are safe for consumers – is a fact and not a matter of assessment.

116. The US further claims (at para. 111) that "[a]s noted by the United States in its Rebuttal Submission, and confirmed by Dr. Boobis' analysis above, even in the artificial scenarios developed by EC scientists, in most cases extreme misuse and overdosing of cattle with implants did not result in violative residue levels, *i.e.*, levels exceeding ADIs and MRLs." This statement is not correct because the new evidence generated by the European Communities does establish that the ADIs and MRLs will be exceeded by the residue levels resulting from misuse or abuse. Since the US (and on this point also Canada) keep arguing that extreme misuse did not result in violative residue levels, it is important to quote the conclusion from the relevant EC study (Exhibit EC-17) which states:

> "Treatement with zeranol and testosterone propionate, even after multiple application, does not cause any problems, as far as infringement of the threshold levels is concerned. Off-label application of trenbolone acetate and estradiol benzoate, however, may lead to illicit values. Exceeding of the MRL was found in the liver in one out of two animals after 3-fold and in two out of two animals after 10-fold dose of the 200 mg-trenbolone acetate-implant. Estradiol threshold levels were violated in the liver and in the kidney even after 3-fold dose of Synovex-H. Fattening of calves with the preparations Synovex-H and Synovex Plus lead to similar residue levels as after Synovex-H or Finaplix-H treatment of heifers".

117. It is therefore misleading for the US to summarise the findings of the study in the way described above.

Canada's comment

118. Canada completely fails to comment on Dr. De Brabander's reply. Instead, Canada merely looks for support in Dr. Boisseau's answer. However, contrary to what Canada tries to present as "what is generally accepted within the scientific community: that scientific data do not deteriorate simply because the passage of time", Canada would have been well advised to address Dr. De Brabander's statement whereby "[t]he implications of not using such (modern) data is that the results of the risk assessment are biased in favour of the "allowance" of hormones." Indeed, new data obviously may lead to different conclusions and it is, therefore, indispensable to update and review constantly scientific evidence. Canada obviously fails to do so.

119. Furthermore, Canada also misrepresents Dr. Boisseau's answer concerning the assessment of hormones. Dr. Boisseau merely stated that "[f]or assessing the growth promoters, JECFA has used the same procedure it has used for all other veterinary drugs". Re-formulated by Canada this statement reads as follows: "[a]s the experts confirm, *the data* and process used for assessing the safety of hormones are the same as those used for other veterinary drugs" (emphasis added). Thus, Canada just by convenience adds the word "data" and it presents this as a commonly held view by "the experts" even though Dr. De Brabander (as the only other experts replying to this question) did not make such a statement. This is just another example on how Canada tries to manipulate the Panel in its presentation of the experts' responses.

Q35. Please comment on the European Communities claim that nearly all the studies referred to in the 2000 JECFA report on MGA date from the 1960s and 70s. Is this correct? Have subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies? [see para. 171 of EC Rebuttal Submission (US case), para. 161 of EC Rebuttal Submission (Canada case), para. 55, including footnote 60 of US First Submission and Exhibits CDA-20, 33, 34 and 35]

US comment

120. The United States concedes that the experts (Drs. Boisseau, De Brabander) have confirmed that the studies relied upon date indeed from the 1960s and 70s (paragraph 49 f its submission). The United States relies on Dr. Boisseau's statement cited above (question 34), which the European Communities considers scientifically unsound for the reasons explained above.

Canada's comment

121. Canada ignores Dr. De Brabander's reply for obvious reasons. But Canada appears also to accept that the data examined by JECFA in 2000 and again in 2004 for MGA date from the 1960s and 1970s.

(c) Dose-response relationship

Q36. How would you describe a dose-response assessment? Is it, as suggested by Canada in para. 78 of its Rebuttal Submission, "widely, if not universally, accepted that adverse effects arising from hormonal activities are dose-dependent"? Is dose-response assessment a necessary component of hazard characterization? Or, is there an alternative approach which can replace the dose-response assessment. Is a dose-response assessment feasible/necessary for substances that are found to be genotoxic or to have genotoxic potential? [see para. 153 of EC Replies to Panel Questions, para. 200 of EC Rebuttal Submission (US case); paras. 143, 154, and 156 of US First Submission, paras. 70-74 of US Replies to Panel Questions, and paras. 34 and 37-40 of US Rebuttal Submission; paras. 76-82 of Canada Rebuttal Submission]

US comment

122. The United States refers to Drs. Boisseau's and Boobis' reply to this question in paragraph 21 of its submission. No reference is made to Dr. Cogliano's reply. Contrary to what the United States claims there is no consensus among the experts on whether a dose-response assessment is a necessary component of hazard characterisation. Indeed, Dr. Cogliano takes the exact opposite view. Also, Dr. Boobis recognises that there may be differences in approach between Europe and the US and Canada as regards the assessment of compounds that have been "identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action."

Canada's comment

123. Although all the experts, including the Codex and JECFA, agree that there are no legally binding risk assessment techniques in the sense of Article 5.1 of the *SPS Agreement* for this kind of substances, Canada makes the unsubstantiated statement (at para. 141) that the hazard-based approach would be inconsistent with the obligations under the *SPS Agreement* that a substance be evaluated for the "potential for occurrence" of an adverse effect. The European Communities finds nothing of this sort in the terms "potential for occurrence", as interpreted by the Appellate Body in the *Hormones* case, given also that a qualitative assessment of the risk is also permissible. In any case, the European Communities has carried out such an analysis of the likelihood of occurrence of the scientifically identified risk in the case of these hormones.

Q37. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "...while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents..."? [see Exhibit CDA-25]

US comment

124. The United States does not refer or comment on the experts' (Drs. Boisseau, Boobis) replies to this question.

Canada's comment

125. The European Communities considers that Canada's statement (at para. 142) that "in light of the universally held view that the adverse effects of hormones are dose-dependent", is erroneous because it is factually not true, as the evidence presented by the European Communities has demonstrated. Indeed, except JECFA and the 2 experts Drs. Boisseau and Boobis who participated in the risk assessment of JECFA, the majority view (which is growing steadily since 1999) is that expressed by the IARC and the 2002 US Carcinogenesis Report that these hormones act by direct and indirect mechanisms.

(d) Sensitive populations

Q38. Please describe the range of physiological (or background) levels of the sex hormones in humans and identify the variations in these levels on the basis of age, sex group, and physiological stages.

US comment

126. The United States refers to Dr. Boisseau's reply to this question in paragraph 65 of its submission, in the context of its comments on the replies given on Question 40 (see below).

Canada's comment

127. Canada pretends that Dr. Boisseau in his reply "raises concerns, as many others have done, about the reliance by the EC on a new 'ultrasensitive biosassay'". However, first of all, Dr. Boisseau has not expressed any "concerns" but he merely said that "[i]t would be important to know whether these new bioassays have been properly validated (…)". Thus, Dr. Boisseau has merely raised a question. Second, Canada refers to "many others" while, indeed, all other experts have not raised any concerns. Canada, therefore, is making a misleading general statement, which is not supported by the facts.

Q39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol-17β and its metabolites resulting from the consumption of meat and meat products presents a potential risk to public health in particular to those groups of the populations which have been identified as particularly sensitive such as prepubertal children" [see para. 147 of the EC Replies to Panel Questions]

US comment

128. The United States refers to the experts' (Drs. Boisseau, Sippel) in paragraphs 67 and following of its submission. Contrary to what is claimed by the United States, Dr. Boisseau does not state that "the EC has failed to assess this risk entirely." Dr. Boisseau merely takes the view that a quantitative dose-response assessment (as opposed to a qualitative one) would have been needed.

129. The United States discusses Dr. Sippel's reply to this question in great detail (in paras. 64-82). As regards the validation of the Klein assay, the principle of the yeast assay has been validated in an international comparative study of different assays for estrogens (Andersen et al., Comparison of short-term estrogenicity tests for identification of hormone-disrupting chemicals. *Environmental*

Health Perspectives; 107 (Suppl. 1): 89-108, 1999, Exhibit EC-123), so this should not now be in doubt. Moreover, how can the US (and Canada on this point) claim that an assay cannot be used because it had not been properly validated, since it is clear that JECFA used old "historic" values for endogenous hormone levels in children that are clearly and undisputedly wrong because the old assays used (RIA) cannot measure such levels? Therefore JECFA used the LIMIT-OF-DETECTION as the "real values" in children, which is obviously wrong and scientifically unacceptable.

130. The US criticise the EC statement "any excess exposure..." but the concept of concentration additivity has been proven for estrogens, including the demonstration of "0+0 ≈ 0" (i.e. that two doses which alone do not produce any detectable effects, when added together result in an observable effect). Thus, any dose matters. On dose additivity see: Rajapakse N., Silva E., Kortenkamp A.: *Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action*, in Envir. Health Perspec. 110, 917-921 (2002) (Exhibit EC – 116); and also Tinwell H., Ashby J.: *Sensitivity of the Immature Rat Uterotrophic Assay to Mixtures of Estrogens*, in Envir. Health Perspec.112, 575-582 (2004) (Exhibit EC – 112).

131. The US criticises (at para. 67) the reply of Dr. Sippell for "proposing a different result than his own research". However, the cited statement from Dr. Sippell is from a 2000 (published in 2001) study, and a lot has happened since then, including the publication of many of the cited papers. Thus, Dr. Sippell demonstrates his scientific integrity by adjusting his opinion according to the developing scientific research. This is contrary to for example Dr. Boobis, who repeatedly claims that his opinion has not changed since 1999, despite the publication since 1999 of so many papers on direct genotoxic action.

132. At para. 68 the US cites the study by *Schmidt* which shows an overall association between estradiol levels and postnatal breast development for the groups as a whole. But the study also shows large variations in estradiol levels, including a demonstration of breast development without measurable levels of estradiol. This emphasises the difficulty in measuring the very low estradiol levels, and the study clearly shows breast development, likely caused by estradiol, also in girls where the estradiol level cannot be determined by the RIA assay. Whether this is a pathological effect cannot be answered before the possible outcome of perturbed breast development (breast cancer) can be assayed (i.e. in 40-50 years), but recent research into the origin of breast cancer do suggest that changes in mammary gland development may play a significant role (see Baik I, Becker PS, DeVito WJ, Lagiou P, Ballen K, Quesenberry PJ, Hsieh C-C.: *Stem cells and prenatal origin of breast cancer*, in Cancer Causes and Control 15: 517–530, 2004).

133. In para. 69 the US discusses the *Lampit et al* study, which clearly demonstrate an effect of the administrated estradiol on the growth of the children. However, the US criticises that *Lampit et al.*, "fails to quantify the amount of estradiol that would be required to accelerate growth in normal children". However, this is a consequence of the lack of sufficiently sensitive assays, since *Lampit et al.* cannot measure the serum levels of estradiol, neither before nor after the administration of estradiol. Thus, *Lampit et al*. clearly show an effect of administrated estradiol, despite serum levels not reaching the current detection limit of the assays. This is very important and an extremely relevant finding which the US avoids to confront objectively.

134. In paras. 70 and 71 the US advances a number of unscientific arguments. It is textbook knowledge that estradiol strongly influences the onset of puberty in girls. Is this questioned by the US and Canada? Given that it is beyond doubt that estradiol is the main determinant for the onset of puberty in girls, it seems reasonable that Dr. Sippell raises the possibility that exposure to excess hormones in the US may play a role for trends in puberty disorders.

135. In para. 73 the US discusses the other publications cited. But in line with many other publications, the *Felner & White paper* clearly shows that a small amount of estradiol strongly affects breast development in children.

136. The US statement in para. 74 contains many aspects that need clarification. First, there are several publications that show higher estrogen levels for twins (1.7 to 3 times higher in a *twin pregnancy* compared to a singleton pregnancy) (Kappel 1985; TambyRaja 1981; Ikeno 1985). Second, there are many publications showing lower estrogen levels in women with preeclampsia (Goldkrand 1978; Long 1979; Shibata 2000). Thus, in the absence of other risk factors for breast cancer that change in exactly the same way as the estrogen levels do in these groups, it is reasonable to correlate the changes in breast cancer risk to changes in the levels of the most likely cause for the changed risk, and that is the differences in estrogen levels. The US asks for mechanistic evidence. However, there are so many peer-reviewed papers relating breast cancer to estrogens. Moreover, the publication by *Baik et al. 2004* (cited above) provides a possible mechanistic explanation, especially when combined with other publications linking the cells described by *Baik et al.* to cell types that are the prime candidates for being the cells-of-origin for breast cancer (for example, Petersen et al., 2003). See on Estrogen levels in twin pregnancies compared to singletons*:* B. Kappel, K. Hansen, J. Moller, J. Faaborg-Andersen: *Human placental lactogen and dU-estrogen levels in normal twin pregnancies*, Acta Genet Med Gemellol (Roma) 34 (1985) (1–2), pp. 59–65; R.L. TambyRaja, S.S. Ratnam: *Plasma steroid changes in twin pregnancies*, Prog Clin Biol Res 69A (1981), pp. 189–195; N. Ikeno and K. Takahashi: *Studies on changes in serum estrone, estradiol, estriol, DHA-S, and cortisol and urinary estriol excretion*, Nippon Sanka Fujinka Gakkai Zasshi 37 (1985) (1), pp. 99–106. See also on Estrogen levels in women with preeclampsia*:* W. Goldkrand: *Unconjugated estriol and cortisol in maternal and cord serum and amniotic fluid in normal and abnormal pregnancy*, Obstet Gynecol 52 (1978) (3), pp. 264–271; P.A. Long, D.A. Abell, N.A. Beischer: *Fetal growth and placental function assessed by urinary estriol excretion before the onset of pre-eclampsia*, Am J Obstet Gynecol 135 (1979) (3), pp. 344–347; A. Shibata, A.Y. Minn. *Perinatal sex hormones and risk of breast and prostate cancers in adulthood,* Epidemiol Rev 22 (2000) (2), pp. 239–248; On breast cancer see: Petersen, O.W., Gudjonsson, T., Villadsen, R., Bissell, M.J., and Ronnov-Jessen, L: *Epithelial progenitor cell lines as models of normal breast morphogenesis and neoplasia*. Cell Proliferation 36**,** Suppl. 33-44 (2003).

137. In para. 76 the US discusses the "Testicular dysgenesis syndrome" (TDS), which describes a HUMAN syndrome that is observed in the clinic! The relationship to animal studies is only made as an attempt to extrapolate possible reasons for the syndrome. In general, animal studies are designed to show effects in a small number of animals and, therefore, large doses are used in order to get effects in essentially all the exposed animals. However, it is a different situation for the human population where TDS-like symptoms are observed in a relatively small percentage of men. Thus, when genetic variation is taken into consideration, low-dose exposure of hundreds of millions of humans may in a small percentage of the exposed people lead to effects similar to those observed at high doses in all the animals in a small group of exposed animals. Moreover, humans are exposed to a mixture of compounds and it has been shown that the effects represent the sum of all the different exposures (i.e. concentration addition!).

138. In para. 77 the US dismisses the effects of DBP because it "is a well known reproductive toxicant". However, DBP in an endocrine disrupter and acts by reducing the testosterone production in the Leydig cells of the testes and thereby DBP is an example of a compound that induces TDS-like symptoms via effects on the endocrine system, by lowering the testosterone levels.

139. Unlike the US comments in paras. 79 and 81, it seems clear that Dr. Sippell's conclusion "exposure during pregnancy might result in severe transplacental virilisation of a female fetus" is reasonable, since it has been shown that trenbolone is about 3 times more potent that testosterone and

given that trenbolone is extensively used as an androgen by body builders. This strongly suggests that trenbolone is a potent androgen in humans.

140. Despite the US comments in para. 80, there are now several studies on the estrogenic potency of Zeranol (e.g. Guevel & Pakdel 2001; Liu & Lin, 2004) and all essentially report the same potency (which is similar to that of estradiol). The *Leffers et al* paper analysed the induction of several estrogen-regulated genes and found that different genes responded differently to the tested estrogens. However, the *Leffers et al.* paper did not measure cell proliferation and none of the analysed genes were proliferation-sensitive. The observation that DES and estradiol (and Zeranol) were equipotent depended on which genes were used for the analysis. The key finding in the *Leffers et al*. paper, which the US apparently fails or does not wish to accept, is that Zeranol is as potent as estradiol and that has now been confirmed by other studies. See in particular: Le Guevel R, Pakdel F: *Assessment of oestrogenic potency of chemicals used as growth promoter by in-vitro methods*, in Hum Reprod. 2001 16,1030-1036 (Exhibit EC – 108); and Liu S, Lin YC: *Transformation of MCF-10A human breast epithelial cells by zeranol and estradiol-17beta*, in Breast J. 2004 10, 514-521 (Exhibit EC – 62).

Canada's comment

141. Contrary to what Canada asserts, Dr. Boisseau is not criticizing the "excess exposure" but merely asks for its assessment and comparison. In other words, by its reply Dr. Boisseau actually confirms that an "excess exposure" exists.

142. In its comments on Dr. Sippell's reply, Canada is making again an unqualified statement concerning the "controversial" bioassay methodology. However, Canada does not offer any supporting arguments for its blunt statement. Furthermore, Canada pretends that "the experts have contested" elsewhere the conclusions of the European Communities' quote. This is not true. Canada would be well advised to respect more accurately the various experts' replies instead of using an unqualified and misleading language in order to manipulate the Panel.

Q40. The European Communities states that "the levels of endogenous production of the hormones by prepubertal children is much lower than previously thought and this finding, which is subsequent to the 1999 JECFA report, casts serious doubts about the validity of JECFA's findings on the dose-response relationship..." Please comment on the methodology used by the SCVPH to support the conclusion that hormone levels are lower than previously thought, and in particular comment on the validity of these methodologies and their conclusions. Would your conclusions have been the same at the time of adoption of the Directive in September 2003?

US comment

143. The United States refers to Dr. Boobis' reply to this question in paragraphs 28, 65 through 67 and 83 of its submission. There is a discussion of Dr. Sippell's view on assay validation in paragraph 66 of the submission, on which the European Communities has already commented above.

Canada's comment

144. Canada refers to the "concerns" by Dr. Boisseau as expressed in its reply to Question 38. However, as already mentioned above, Canada is not accurately interpreting Dr. Boisseau's reply and it abuses the expert's response to pursue its own litigation objective. In the same vein, it is quite superficial when Canada, in paragraph 150, refers to "concerns highlighted by the experts about the SCVPH's use of this methodology". If at all, there is only one expert, Dr. Boobis who makes some critical remarks, while Dr. Boisseau remains neutral, Dr. Sippell supports the methodology and Dr. Guttenplan, Dr. Cogliano and Dr. De Brabander do not express themselves at this stage. Even

more, Dr. Guttenplan, in his response to Question 52 states that: "[a]lthough the US and Canada question the accuracy of the assay originally employed for estrogens at the low levels found in children, recent reports (…) indicate more recently reported levels used by the EC are accurate".

145. Concerning the in vitro assay developed independently by Klein *et al* and F Paris *et al* to assay low amounts of receptor-active estrogens, it should be added to what has been explained above that these biological assays are not absolute in the sense that they should give precise and absolute values. Indeed, they are internally validated assays but not yet inter-laboratory comparison has been made. But even if one may consider that this is a drawback, the assay is very useful in that it is far more sensitive than any other spectro-physical assay based on mass spectrometry. Nevertheless, this inter-technique comparison will be performed rather soon thanks to the new generation of mass spectrometry based on Fourier-Transformed MS. This technological progress should be useful to perform the complete hormonal exploration (androgens, estrogens) in plasma of no- and pre-pubertal girls and boys and the results will be critical to the risk assessment exercise. Conversely, the JECFA evaluation was based on old and very questionable data that were not produced at that time by any spectro-physical method but only by radio-immunologic assays.

Q41. Why would individuals with the lowest endogenous hormone levels be at greatest risk? How would the risks for these individuals arising from hormones naturally present in meat differ from the risks arising from the residues of hormone growth promoters?

US comment

146. The United States does not dispute the experts' (Drs. Boisseau, Sippell) replies to this question, which confirm the view taken by the European Communities that prepubertal children are particularly sensitive to hormones exposure.

Canada's comment

147. As in its comments on earlier question, Canada claims support by "the experts" for the criticism on the Klein assay which, however, is not supported by the facts. Thus, Canada's criticism on the detailed reply by Dr. Sippell is completely baseless.

Q42. To what extent, in your view, has JECFA taken into account the particular situation of sensitive populations, in particular prepubertal children, in its risk assessments with respect to oestradiol-17β? Please compare the original data concerning endogenous production of natural hormones by prepubertal children upon which JECFA based its assessment and those used by the European Communities in its risk assessment. In your view, does the scientific material referred to by the European Communities require a revision of the Codex recommendation with respect to oestradiol-17β? [For the questions in this section, see paras. 121-122 of EC Rebuttal Submission (US case), para. 103-104 of EC Rebuttal Submission (Canada case), Exhibits EC-88, 99, paras. 42-45 of US Rebuttal Submission, paras. 84 and 159 of US First Submission, and for JECFA's work Exhibits CDA-11, 16, 17, 18, 39]

US and Canada's comments

148. The United States refers to Dr. Boobis' and Sippell' replies to this question in paragraphs 67, 84 and 85 of its submission (no reference to Dr. Boisseau). In Footnote 178 of its submission, the United States dismisses Dr. Sippell's view that JECFA has not adequately taken into account the particular situation of sensitive populations, in particular infants and prepubertal children. The United States claims that it is unclear whether Dr. Sippell is familiar with JECFA's safety factors or whether/why he finds these factors to be inadequate. However, none of the US comments is valid because the so-called safety factors cannot substitute for the need of JECFA to review these hormones

on the basis of the most recent scientific data, including in particular the direct genotoxicity and the low levels of endogenous production by prepubertal children.

149. Similarly, Canada fails to address Dr. Sippell's detailed and supported criticism of the JECFA conclusions. The European Communities regrets Canada's selective perception of all experts' replies and to respond adequately to criticism on the use of hormones as growth promoters.

(e) Bioavailability

Q43. Please define bioavailability, comment on the significance of bioavailability to assessments of risk, and on the degree of bioavailabilitiy of the residues of the hormones at issue when consumed in meat, taking into account parties' differing views on this matter. [see paras. 123-124 of EC Rebuttal Submission (US case), paras. 105-106 of EC Rebuttal Submission (Canada case), paras. 100, 155-159 of the EC Replies to Panel Questions, paras. 32 and 41-42 of US Rebuttal Submission, paras. 69, 71, 88-89 and 146 of US First Submission, and para. 134 of Canada Rebuttal Submission]

US comment

150. The United States claims that "none of the experts' responses appear to indicate otherwise", when claiming that the European Communities has failed to take into account the low bioavailability of estradiol 17β in its assessment of that hormones (see paragraph 27 of its submission). This is plainly wrong as Dr. Guttenplan comes to the opposite conclusion when stating that: "[i]t appears that the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account. (Estrone is readily inter-convertible with estrogen). Calculations are presented in the above reference that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children (EC Rebut, para. 122). This would represent a risk factor (EC Rebut, para. 122)."

151. Indeed, the United States tries to refute the view taken by Dr. Guttenplan by arguing that (1) he relies on materials cited by the European Communities that do not in fact demonstrate a higher bioavailability for estradiol 17β than previously thought, and (2) he miscasts as "paradoxical" a US argument relating to bioavailability (paragraphs 28 and following of the US submission).

152. As for the first argument, it should be recalled that human beings are considered as having a monogastric physiology and, consequently, the large digestibility of nutrients should be clearly applicable. Therefore, for risk assessment purposes it is considered that digestibility and hence bioavailability of steroids ("primary bioavailability" or the amount of xenobiotics absorbed from a given matrix or formulation) and in particularly estrogens is more or less complete. In the absence of any specific study on bioavailability of steroids considering the low amounts of residues found in edible tissues of treated cattle, there is a need to consider this bioavailability parameter at its maximal value due to a complete intestinal absorption. This point has been formerly anticipated in milk-fed calves which have kept a seemingly monogastric physiology and for which the estrogens excretion is mainly achieved by urinary route, that is strikingly different from this obtained for ruminant physiology, which prove the important entero-hepatic cycle and hence the very significant intestinal absorption of estrogens. This also explains the bioavailability of hormones present in gut, even if they are excreted by the biliary route. In addition, there is a need of common understanding of what is the definition of bioavailability of steroidal hormones, given the greatly varying degrees between gut, liver and peripheral tissues, due to the progressive metabolism of those hormones. Again, we need to consider that there is total intestinal absorption and a complete hormonal effect at least on intestinal cells and hepatocytes before their metabolic degradation. Therefore, it is very doubtful when JECFA and Dr. Boobis assume that an oral bioavailability of rate of 5% (Fortherby, 1996) is rightly used in

order to assert there is a low hormonal effect of orally given hormones. This result may be only a comparative result of hormonal effect of two different administration routes on classically considered target tissues and is related to raw bioequivalence measured on a given target tissue, not the bioavailability. In the context of hormone residues in meat, no specific results have been obtained on the hormonal response of intestinal cells exposed to those hormonal residues neither on hepatic cells measurements have been carried.

153. Some specific attention should also be placed on the different bioavailability rates of estrogens, considering that some are ingested as free or conjugates compounds (thus being easily hydrolyzed by gut microflora) and some other are lipophilic compounds (estrogen esters) and are susceptible to take the lymph route after intestinal absorption (see Paris et al, 2000). Therefore, this class of lipoidal estrogenic residues will partially escape the liver degradation step. This specific bioavalability of estrogen esters may explain why, even by oral route administration, they are about 10 fold more active than estradiol in inducing a significant uterotrophic response in the juvenile female rat model (Paris et al, APMIS 109 (2001) 365-375) (Exhibit EC-117). This has been taken into account by the SCVPH, unlike JECFA and Dr. Boobis that seem to disregard it.

Canada's comment

154. Canada fails to address specifically the conclusion by Dr. Guttenplan whereby "calculations are presented in the above reference that suggest that even with low percentages of bioavailability of estrogen, the levels in meat could result in bioavailable estrogen approaching the daily production rate of oestradiol in pre-pubertal children (EC Rebut, para. 122). This would represent a risk factor (EC Rebut, para. 122)".

(f) Good veterinary practice (GVP)

Q44. Please define "good veterinary practice" (GVP) and/or "good practice in the use of veterinary drugs" (GPVD). What are the relevant Codex standards, guidelines or recommendations relating to GVP/GPVD? Please comment on the statement by the European Communities that the definition of the GPVD is "circular and hence problematic." [see para. 88 of the EC Replies to Panel Questions]

US comment

155. The United States does not comment on this point and the replies given by Dr. De Brabander and Dr. Boisseau (on the discussion in paragraph 107 of its submission see below, question 45).

Canada's comment

156. Canada, regrettably, does not address Dr. De Brabander's reply on why the definition of the GPVD is considered to be "somewhat circular and hence problematic". Instead, Canada just reproduces a general statement by Dr. Boisseau although even Dr. Boisseau provides an interpretation which Canada, again, ignores.

Q45. In conducting a risk assessment of specific veterinary drugs, what assumptions are made concerning GVP, if any? How, if at all, are risks that might arise from the failure to follow good veterinary practice in the administration of veterinary drugs addressed?

US comment

157. In the context of this question the United States comments on the reply given by Dr. De Brabander in paragraph 107 of its submission dismissing the reference he makes to evidence

of abuse of hormonal substances in the US. While the study referred to by Dr. De Brabander is certainly interesting, the European Communities would recall that it has undertaken its own studies to assess the possibility of misuse and abuse in the US and Canada. It is on these studies that the EC risk assessment relies on.

Canada's comment

158. Canada does not comment on Dr. De Brabander's pertinent response whereby "farmers (and vets) have indeed economic incentives to misuse growth promotion substance (implants or others)". The Panel may draw its own conclusion by this Canadian failure.

Q46. To what extent were risks from misuse or abuse assessed by JECFA in its evaluation of the hormones at issue? In terms of the three synthetic hormones at issue, how is GVP relevant to the establishment of MRLs by JECFA?

US and Canada's comments

159. The United States and Canada does not refer to or discuss in detail the experts' (Drs. De Brabander, Boisseau, Boobis) replies to this question.

Q47. How significant are any differences in GVP in the European Communities, the United States, and Canada? Does the EC risk assessment take into account relevant control mechanisms with respect to GVP in place in the United States and/or Canada? If so, what are their conclusions?

US and Canada's comments

160. The comments above under Question 45 apply here as well. In addition, Canada argues (at para. 182) that the comment of Dr. De Brabander that control mechanisms short of total ban is "deeply flawed". However, Canada - as well as the US – fails to discuss at all the numerous instances of abuse and misuse documented in the EC inspections in their territories, nor do they comment on the findings of the evidence reported in exhibits EC-67 to 73.

Q48. To what extent does the scientific evidence referred to by the European Communities assess risks to human health from residues of misplaced implants or improper administration, i.e. when administered differently than indicated on the label of the manufacturer or contrary to GVP, of any of the six hormones? Would your reply have been different at the time of adoption of the EC Directive in September 2003? What are the potential hazards, if any, to human health of the use of large quantities, or doses higher than recommended, of any of the six hormones in dispute?

US comment

161. The United States refers to the experts' (Drs. Boobis, De Brabander, Boisseau) replies to this question in paragraphs 103, 104 and 109 of its submission. As stated in its own comments, the conclusions reached by Drs. Boisseau and Boobis rest on the assumption that a quantitative assessment is required. Indeed, Dr. Boobis concedes that this is not the view taken by the EC risk assessors, a remark which the United States conveniently omits to refer to or comment on. The US criticises the statements by Dr. De Brabander as not based on evidence, but as explained above in relation to Question 47 the evidence is provided in the relevant EC exhibits which the US has chosen to ignore.

Canada's comment

162. The way Canada comments on the three expert replies is again an interesting and typical example on how Canada attempts to influence the Panel by a selective reproduction of only those expert replies which, in Canada's view', supports its position. However, instead of looking for comfort in replies that merely allegedly confirm its own position (which is a natural and convenient way of doing but insufficient in this case) Canada should have better addressed Dr. De Brabander's very critical conclusion whereby "more and more scientific data sustain the ban on the use of hormones: the economical profits resulting from using hormones does not balance the potential danger [in respect of, *inter alia*, animal welfare, environment and transformation of hormones] **in all of its aspects**" (emphasis in the original).

Q49. What analytical methods, or other technical means, for residue detection in tissues exist to control the use of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice? What tools are available to control the use by farmers of the six hormones in dispute for growth promotion purposes in accordance with good animal husbandry practice and/or good veterinary practice?

US comment

163. The United States does not refer to or discuss Dr. De Brabander's reply to this question. Moreover, as the European Communities has explained, these hormones are dispensed over the counter (OTC) in the US and Canada. In such a case the concept of GVP is not applicable and can be even misleading. Veterinarians are not involved in the whole process of distribution and administration of these hormones to animals since any farmer is free to use them at his will. Therefore, the initial statement by Dr. Boobis that "… it has been used as an anabolic agent in veterinary practice" is totally misleading as regards the realistic conditions of use of these hormones in the US and Canada. Moreover, the pinna of the ear is the only authorized site of application.[9] If this is not observed, the depot goes directly into the edible part of the animal. Thus, it is more than surprising that this issue of utmost importance is not covered by any reply from the defending parties and the experts. Dr. Boisseau states that the administration of the implant is "… by subcutaneous implant to the base of the ear …". If this is so, this is already a serious misuse of these implants.

Canada's comment

164. The European Communities agrees that the additional information asked by Canada may be asked from Dr. De Brabander. The European Communities is confident that this also will support its position.

Q50. Are there other measures available to the European Communities (other than a complete ban) which could address risks arising from misuse and failure to follow good veterinary practice with respect to the use of the hormones at issue for growth promotion purposes? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why?

[9] See in the US the freedom of information summary, supplemental new animal drug application, NADA 140-897; Route of Administration: Subcutaneous implantation on the posterior aspect of the middle one-third of the ear by means of an implant gun; and freedom of information summary, supplemental new animal drug application, NADA 140-897, the Center for Veterinary Medicine has concluded that, for these products, adequate directions for use by layperson have been provided and the products will have over-the-counter (OTC) status. Label directions are accompanied by pictorial diagrams and detailed instruction in plain language. The drugs are not controlled substances. The products' status remains OTC. The labelling is adequate for the intended use and has sufficient warnings/statements to prevent illegal use in veal calves.

US comment

165. The United States does not refer to or comment on Dr. De Brabander's reply to this question, which is entirely supportive of the position taken by the European Communities.

Canada's comment

166. In its comments on Dr. De Brabander's reply Canada fails to see the difference between, on the one hand, the theoretical possibilities of control possibilities, as provided by Dr. De Brabander in his reply to Question 49, and the actual possibility to address risks arising from misuse and the failure to follow GVP and which, in Dr. De Brabander's view, can only be achieved by the European Communities through a complete ban. There is no contradiction between these two statements.

Q51. Does the material put forth by the European Communities regarding misuse or abuse of the hormones at issue in the United States and Canada call into question the potential applicability of Codex standards with regard to imports of meat from cattle treated with hormones from the United States and Canada? [For questions on GVP see the SCVPH Opinions in Exhibits US-1, 4 and 17, paras. 125-127 of EC Rebuttal Submission (US case), paras. 107-109 of EC Rebuttal Submission (Canada case), para. 154 of EC Replies to Panel Questions, Exhibits EC-12, 67, 68, 69, 70, 73, 96, 102, 103, paras. 32 and 54-65 of US Rebuttal Submission, para. 75 of US First Submission, paras. 107-111 of Canada Rebuttal Submission, page 40 of Exhibit CDA-27]

US comment

167. The United States refers to Dr. Boisseau's reply in paragraph 108 and comments on Dr. De Brabander's reply in paragraph 111 of its submission. The US relies again on the statements by Dr. Boobis (in paras. 109-110) to counter the evidence on abuse and misuse produced by the European Communities. But neither Dr. Boobis nor the US contest as such the accuracy of the scientific findings reported in those studies. Dr. Boobis' only claim is that (at para. 109) that the "probability" of these happening is "extremely low". However, what is "extremely low" is not defined nor is it true of course.

Canada's comment

168. Canada draws the conclusion from Dr. Boisseau's reply that "in the unlikely event that GVP is not followed, the applicability of Codex standards is not put into doubt". However, Dr. Boisseau never said this. Rather, Dr. Boisseau explicitly agreed that "the European Communities is right to state that, in case of these different misuses/abuses, the exposure of consumers may be totally different" (Dr. Boisseau's reply to Question 48).

(g) Other

Q52. Do the risk assessment of the European Communities or any other scientific materials referred to by the European Communities demonstrate that a potential for adverse effects on human health arises from the consumption of meat from cattle treated with any of the six hormones in dispute for growth-promotion purposes? If yes, why? If not, what kind of evidence would be required to demonstrate such potential adverse affects? Would your response have been different at the time of adoption of the Directive in September 2003?

US comment

169. Apart from a wholesale reference to Dr. Boobis' reply in footnote 41, the United States does neither refer to nor discuss the experts' (Drs. Boobis, Boisseau, Guttenplan) replies to this question.

Canada's comment

170. Canada attempts again to mislead the Panel by drawing conclusions that are not warranted, in particular when it misstates (at paras. 197-198) the reply of Dr. Guttenplan. If to the reply by Dr. Guttenplan are added the replies from the other 3 scientists who replied in their areas of expertise, then 4 out of the 6 scientists, in the view of the European Communities, agree with its scientific basis and the risk assessment it has conducted on these hormones. The European Communities would suggest that the Panel requests each of the experts to respond to this question for his respective areas of expertise.

Q53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol-17β or other oestrogenic compounds in commercial preparations? Would the systematic use of these and the synthetic hormones in combination have any implications on how the scientific experiments and the risk assessments are to be carried out? If so, have the scientific materials referred to by the European Communities or relevant JECFA reports taken into account the possible synergistic effects of such combinations on human health? [see sections 4.2-4.3 of the Opinion of the SCVPH of 2002 in US Exhibit 1]

US comment

171. The United States does neither refer to nor comment on the experts' (Drs. Boisseau, Guttenplan) replies to this question.

Canada's comment

172. Canada's statement is, to say the least confusing. First, Canada pretends that Dr. Boisseau and Dr. Guttenplan "advise that the exposure to these hormones, both alone and in combination is so low that there is very little risk of any increase in the risk if assessed in combination". Yet, this description falls short by what Dr. Boisseau or Dr. Guttenplan actually stated. Dr. Boisseau merely states that "[c]onsidering that it has been established that progesterone and testosterone are not genotoxic, it is not likely that the testing of combinations of progesterone and testosterone with oestradiol-17β would have led to synergistic effects compared with those obtained from these individual substances". Dr. Guttenplan, for his part, states that "the use of mixtures should complicate risk assessment/scientific experiments, as they would have to evaluate/investigate each component alone and in combination. This is a major undertaking as effects of individual agents may be additive, inhibitory, and synergistic or there may no effect. It appears from the evidence submitted that, by far, estrogen is the major agent of risk and because the concentrations of all of the hormones in beef are so low, that they would be unlikely to affect the potency of estrogen. However, it appears that no experiments on effects of combinations were performed, so some uncertainty exists here".

173. Against this background, Canada's conclusion that "once oestradiol 17β has been demonstrated not to have effects when used as a growth promoter, there is little risk that adverse effects would occur if used in combination with the other hormones" has never been stated by any of the experts.

Q54. What is the acceptable level of risk reflected in the Codex standards for the five hormones at issue? How does this compare to the European Communities' stated objective of

"no risk from exposure to unnecessary additional residues in meat of animals treated with hormones for growth promotion". [see para. 149 of EC Rebuttal Submission (US case)]

US comment

174. The United States does neither refer to nor comment on the experts' (Drs. Boisseau, Boobis, Guttenplan) replies to this question.

Canada's comment

175. The comments by Canada about "theoretical" and "real" risk are again misleading, because the scientists (Drs. Guttenplan, De Brabander and Sippell) and the European Communities have identified a real risk from the consumption of residues in meat from animals treated with these hormones for growth promotion purposes. The existence of the real risk has been confirmed also by the US 2002 Carcinogenesis Report and it is simply a question of defining the appropriate level of protection – which is much lower in the US and Canada than in the European Communities – that has so far led the defending parties from ignoring the regulatory implications of that finding. This is not different from what has happened in the case of Carbadox a few years ago, when the defending parties were arguing this case in 1997 before the WTO. It is useful to recall here how Canada has explained its 360 turn on Carbadox in 2000, just 3 years after its persistent insistence in the WTO that Carbadox was a safe substance to use:

> "Carbadox is an antibiotic approved in the 1970s for use in swine to prevent and treat disease as well as to maintain weight gain during periods of stress, such as weaning. It has been shown that the drug, and the by-products of the drug that occur when the drug is metabolized in the body, can cause cancer in rats. However, when an appropriate withdrawal period (i.e stopping the administration of the drug before slaughter) is observed, the drug and its breakdown products are not found in the food derived from the treated animal. Carbadox was approved on the basis that this specified 35-day withdrawal period be strictly observed.
>
> However**, reports of misuse and accidental contamination**, combined with **a better scientific capacity** to detect breakdown products of carbadox, resulted in serious concerns about the safety of the product. The first reported incident occurred in the fall of 2000 when pigs at a farm in Quebec were accidentally fed carbadox and slaughtered without respecting the withdrawal period. All affected product was recalled and removed from store shelves and an investigation into the incident was launched. The investigation was then broadened to review the use of carbadox throughout the Canadian pork industry.
>
> In February 2001, responding to the European Union Fall 2000 audit of the Canadian Program for the Control of Residues, Canada made a public commitment to reassess the use of carbadox in pigs.
>
> Based on the reassessment, Health Canada proposed to amend the Food and Drug Regulations to ban the sale of any drug containing carbadox for administration to food-producing animals."[10] (Emphasis added)

Q55. Do the Opinions of the European Communities or other scientific materials referred to by the European Communities evaluate the extent to which residues of growth promoting

[10] See at the website of Health Canada at: http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2001/2001_88_e.html, visited on 11 July 2006.

hormones in meat contribute to what the European Communities calls "additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings"? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 151 of EC Replies to Panel Questions, paras. 43-44 of US Rebuttal Submission, paras. 83-85 of Canada's Rebuttal Submission]

US and Canada's comments

176. The United States refers to Dr. Boisseau's and Dr. Guttenplan's replies in paragraphs 23 and 25 of its submission but fails to put in doubt the accuracy of Dr. Guttenplan's comments. The fact is that the decision of JECFA to set an ADI for oestradiol 17β was based on the alleged lack of evidence for *in vivo* genotoxicity and the seemingly safe use of oral contraceptives and postmenopausal estrogen replacements, implying the existence of a threshold for the carcinogenic effect of oestradiol 17β. But both situations are wrong and in any case have changed in the meantime, as there is now clear evidence for *in vivo* genotoxicity and evidence for an increased risk of cancer in women taking oral contraceptives and postmenopausal estrogen therapy. Even if a threshold would exist (which should not because of genotoxicity), the endogenous production of oestradiol 17β obviously exceeds that threshold, because we see oestrogen mediated cancer of the breast, endometrium and ovary in women. So any additional exposure to estrogens, e.g. from food, will inevitably increase the risk.

177. Moreover, as the EC has explained above, the US criticism that the EC statement "any excess exposure would increase the risk" is incorrect because the concept of concentration additivity has been proven for estrogens, including the demonstration of "0+0 ≈ 0" (i.e. that two doses which alone do not produce any detectable effects, when added together result in an observable effect). Thus, it is clear that any dose matters.

Q56. Has JECFA/Codex considered in its risk assessment of the five hormones such "additive risks? Are there internationally recognized guidelines for conducting assessments of "additive risks"?

US comment

178. The European Communities suggests that it be clarified at the hearing where in its assessment JECFA is considering the issue of additive risks. United States refers to Drs. Boisseau's and Boobis' reply to this question in paragraph 26 of its submission, but again uses the idea of "trivial increase, something it is obviously unable to prove with scientific evidence. Indeed, quite the opposite is true. It has been shown that additivity of an exogenous dose to an endogenous hormone that is already causing responses will increase risk and have no threshold (see Hoel, D.G., Incorporation of background in dose-response models, in Fed. Proc. 39, 73-75 (1980)). Nonetheless, non-linearity (a threshold) is assumed.

Canada's comment

179. Canada's comments on the expert' replies only tell half of the story. Indeed, Canada fails to see that Dr. Boisseau stated that for the synthetic hormonal growth promoters, JECFA/CODEX did not consider such "additive risks" probably because no internationally recognized guidelines for conducting assessment of "additive risks" exists. Canada's comment cites with approval Dr. Boobis reply. But the "additive" risk they both have in mind is quite different from the additive risk the European Communities has explained. For both of them, JECFA is supposed to take into account such risks through the mechanism of "safety margins" and default assumptions, which are obviously totally inadequate and scientifically inappropriate for this type of genotoxic substances.

Q57. Canada comments that "one single molecule that the European Communities considers so dangerous from meat derived from animals treated with hormone growth promoters is suddenly not at all that dangerous when consumed from meat from animals treated for therapeutic or zootechnical purposes. The European Communities' concern about the genotoxic potential of oestradiol-17β suddenly and inexplicably disappears." To what extent are hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic or zootechnical purposes, taken into account by the European Communities, if at all, in its assessment of the cumulative effects from the consumption of meat containing residues of the hormones at issue? Would your reply have been different at the time of adoption of the EC Directive in September 2003? If so, why? [see para. 97 of Canada Rebuttal Submission; paras. 17-20 of US Opening Statement]

US comment

180. The United States refers to the experts' (Drs. Boisseau, Boobis, Guttenplan) replies to this question in paragraph 24 of its submission. Contrary to what the United States claims, Dr. Guttenplan does address the Panel's inquiry, i.e. whether the European Communities, in its Opinions, took these treatments into account in an assessment of cumulative effects. He states that the European Communities "does not really take [these] […] into account in their risk assessment." Dr. Guttenplan then refers to the reasons why this is so and qualifies these as "a reasonable response."

Canada's comment

181. Canada draws the wrong conclusion from the expert's reply when it purports that "the experts' advice indicates that the EC is trying to have it both ways: that hormones are genotoxic for some purposes and not others". Indeed, while Dr. Boisseau is questioning the logic of the EC's limited exception for the use of hormones for zootechnical and therapeutic reasons, Dr. Guttenplan expressly states its support for the EC' approach. This is not a question about the genotoxicity of hormones, as Canada tries to present it, but it is a pure risk management decision whereby in these limited circumstances it is assumed that the hormones will not enter into the food chain and, therefore, logically not present a risk to consumer's health. For this reason, it is by the way also an incorrect conclusion by Dr. Boisseau that this limited exception would raise questions regarding the overall approach taken by the European Communities. Indeed, the European Communities has always been pursuing the objective of health protection. This objective is not put into danger in case of the use of these hormones for zootechnical and therapeutic reasons, which in any case has been rejected by the Appellate Body back in 1998.

Q58. Please comment on the EC statement in para. 94 of the EC Replies to Panel Questions that "the only rationale that can be inferred from the available scientific data is that the higher the exposure to residues from these hormones, the greater the risk is likely to be", taking into account para. 105 of Canada Rebuttal Submission.

US comment

182. The United States refers to the experts' (Drs. Boobis, Guttenplan, Boisseau) replies to this question in paragraphs 24 and 25 of its submission. Quoting Dr. Guttenplan as referring to an "indeed very weak statement of the EC", it conveniently omits the rest of Dr. Guttenplan's statement who went on to say "[h]owever, the alternative would be to suggest a risk that might be wildly inaccurate, due to the limitations imposed by the lack of solid data on levels of hormones in meat. Perhaps a better approach would have been to suggest several scenarios. These could be validated or disproved by subsequent studies." Thus, Dr. Guttenplan suggests that other alternative scenarios. The European Communities considers that the Panel may request Dr. Guttenplan to explain what other scenarios he has had in mind.

Canada's comment

183. The comment by Canada (at para. 210) is also incomplete and partly false, because the European Communities has demonstrated that if the appropriate levels of endogenous production are taken into account, the ADIs set by JECFA will be reached and will be even exceeded easily.

Q59. Does the scientific evidence referred to by the European Communities identify any adverse effects on the immune system from the consumption of meat from cattle treated with the growth promoting hormones at issue? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [see para. 132 of Canada Rebuttal Submission]

US and Canada's comments

184. The United States refers to the experts' (Drs. Boobis, Boisseau and Guttenplan) replies to this question in paragraph 86 of its submission. Canada discuss this in para. 211 of its submission. They both do not comment on the fact that there is a straightforward contradiction in the statements they quote. While Dr. Boobis denies that there is any evidence of adverse effect on the immune system, both Dr. Boisseau and Dr. Guttenplan acknowledge that there is such evidence.

Q60. Does the scientific evidence referred to by the European Communities identify and evaluate whether there is a difference in terms of potential adverse effects on human health from the consumption of meat from cattle treated with hormones for growth promotion purposes when these hormones are administered as feed additives (MGA) or implanted? Are you aware of any differences?

US comment

185. The United States only refers to Dr. Guttenplan's reply to this question. In footnote 114 of its submission it states that Dr. Guttenplan's statement that MGA can be administered both as feed additive or implant is incorrect.

Canada's comment

186. Canada's claim (at para. 212) that Dr. Boobis is right in arguing that misuse would "not occur in feed additives" is without any basis. The example of Carbadox may be again useful, because this substance too was administered as a feed additive. But as the European Communities has explained above in relation to Question 54, Canada has admitted that its misuse has occurred and actually to such an extent as to lead it to ban this product also on this ground

Q61. In your view and in the light of information provided by the parties as well as the work undertaken at JECFA and Codex, did the scientific evidence available to the European Communities at the time it adopted its Directive (September 2003) allow it to conduct an assessment (quantitatively or qualitatively) of the potential for adverse effects on human health arising from the consumption of meat from cattle treated with (a) progesterone; (b) testosterone; (c) trenbolone; (d) zeranol; and (e) melengestrol acetate? Would your response differ in light of the scientific evidence provided which is subsequent to the adoption of the EC Directive?

US and Canada's comments

187. As so often, the United States' claim that "*the* experts' responses confirm that the scientific evidence and information relating to the five hormones is sufficient to conduct an assessment" does

not reflect the reality of what the experts have said. Indeed, only Dr. Boobis has taken this view (paragraphs 48 and 49 of its submission).

188. Dr. Boisseau declines to comment on the question itself noting that "I don't really know what were the data available to the European Communities at the time it adopted its directive." Furthermore, Dr. Guttenplan takes a very nuanced and partly opposite view. As regards Trenbolone and Zeranol, he states that from the data available at the time of the Directive, the potential for adverse effects could not be ruled out. The United States tries to undermine this statement by pointing out that Dr. Guttenplan mistakenly thinks that trenbolone is an estrogen.

189. However, Dr. Guttenplan may not be wrong completely as *Bauer et al.* have documented that trenbolone has three separate hormonal activities combined in one substance. It binds to the androgen receptor, progestin receptor and glucocorticoid receptor. This was not documented before. Dr. Boobis and certainly the US (at para. 49) in their statements still call trenbolene an androgen. The finding above is of clear relevance for the risk assessment of trenbolone acetate. If multiple hormonal activities are exhibited from one and the same compound, the potential of the synergistic activity has to be considered. See Bauer ERS., Daxenberger A., Petri T., Sauerwein H. and Meyer HHD.: *Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and to the bovine progestin receptor*, in APMIS 108: 838-846, (2000)(Exhibit EC – 15).

190. The European Communities would disagree however with the statement by Dr. Guttenplan that the evidence for MGA and its assessment "seems sound" and would like that the Panel requests Dr. Guttenplan to provide a more detailed explanation of his statement on this point, taking into account in particular the new evidence produced by the European Communities.

191. The European Communities considers that also the other experts who have not expressed an opinion on this question should be requested by the Panel to take a position in their own areas of expertise, since it seems to the European Communities – from their replies to the other questions – that in their view the evidence available did not allow the European Communities to conduct a full and complete risk assessment.

Q62. Does the scientific evidence relied upon by the European Communities support the EC contention that the new scientific studies that have been initiated since 1997 have identified new important gaps, insufficiencies and contradictions in the scientific information and knowledge now available on these hormones such that more scientific studies are necessary before the risk to human health from the consumption of meat from cattle treated with these hormones for growth promotion purposes can be assessed? Would your reply have been different at the time of adoption of the Directive in September 2003? If so, why? [Please see the following references for the two questions above:

- **paras. 58-94 and 125-129 of US First Submission, paras. 28-32 of US Rebuttal Submission**
- **paras. 116-124 of Canada First Submission, paras. 74, 130-135 of Canada Rebuttal Submission (Exhibit CDA-23)**
- **paras. 108, 147, 162-169 of EC Replies to Panel Questions, paras. 143-174 of EC Rebuttal Submission (US case), and paras. 148-166 of EC Rebuttal Submission (Canada case)**
- **Exhibit CDA-32 provides a detailed table outlining the chronology of JECFA's assessment of these hormones and the resulting documentation]**

US and Canada's comments

192. The United States refers to the experts' (Drs. Boisseau, Boobis and Guttenplan) replies to this question in paragraphs 49 through 53, 90, 103, 109 and 110. As so often, it pretends that "*the* experts' replies" confirm its view where only one or two have done so and another one has taken the opposite view (paragraphs 51 and following). Indeed Dr. Guttenplan has listed a number of examples where the 17 studies have identified important gaps. The United States claims that the majority of those relate to oestradiol 17β and therefore are not relevant for the purposes of the provisional an on the other five hormonal substances (paragraph 52). This allegation is erroneous.

193. In particular, it is again useful to review some of the comments provided by Dr. Boobis for each of the studies funded by the European Communities in order to determine their relevance and the gaps and level of uncertainty they have established.

194. Concerning the study "re: experimental studies in rabbits by Rajpert-De Meyts et al.", only a part of the study concerning metabolism and placental transfer has been published so far (Lange et al. Xenobiotica 2002). The results on the reproductive effects of Zeranol (ZER), Trenbolone Acetate (TBA) and Melengestrol Acetate (MGA) in rabbits exposed during development were summarized in a detailed report (by Rajpert-De Meyts et al.) sent to the European Communities in December 2001 with additional data supplemented in the spring 2002. The study has not yet been submitted for publication elsewhere for the following reasons:

- similar findings concerning the effects of ZER and Estradiol on spermatogenesis and epididymal reserves were previously published in another animal model (bull) by Veeramachaneni et al. Environ & Appl Toxicol 1988; 10: 73-81, thus this part of the rabbit study was only confirmatory;

- in the course of the rabbit study, hundreds of samples of tissues, sera and semen were collected and stored, and only a part of investigations have been completed due to lacking funds. Some ensuing studies are still in progress. The study will be submitted for publication when these investigations have been finalized.

195. The evaluation of the *Lange et al.* study and the report (Rajpert-De Meyts et al.) by Dr. Boobis is one-sided. The sentence stating that *"there was no net accumulation of the compounds in fetal tissues"* is only partially true. The concentrations of the residues after MGA treatment were in fact higher in the fetal muscle than in the maternal muscle, the fact not mentioned by him.

196. The unpublished part of the study of the exposure at three different developmental stages provided a wealth of data, which are dismissed by Dr. Boobis with a following statement: *"It is not clear whether the changes observed were consistent and hence compound-related as only a single dose was used for each compound* ". The report did, in fact, very clearly state that the study was preceded by a dose-finding pilot study that investigated three different doses of all three compounds. Because the higher doses caused extensive adverse changes, only the lowest doses were selected for the definitive study. Contrary to Dr. Boobis' statement - *"nor is it apparent whether the magnitude of all changes discussed reached statistical significance*" - a detailed statistical analysis was performed, with all significant changes at $p<0.01$ and $p<0.05$, showing effects of the anabolic steroid used, clearly highlighted in the report.

197. Concerning the study "re: genotoxic potential of xenobiotic growth promoters and their metabolites", it is true that this study has not provided clear evidence for the genotoxicity of trenbolone, melengestrol acetate and zeranol in several in *vitro test* systems. However, the metabolism studies have clearly shown that all three compounds give rise to numerous hitherto unknown metabolites, which may or may not have adverse effects. Therefore, the value of this study is the

demonstration that the fate of all three xenobiotic growth promoters in the organism may be far more complex than previously thought. Unfortunately, none of the novel metabolites could be structurally elucidated in the limited time period of the study, which prevented publication in peer-reviewed journals. Nonetheless, the structures of these novel metabolites and their biological activities need to be further studied in order to improve the risk assessment. The same applies to the observation of DNA adduct formation, though at low level, of trenbolone in rat hepatocytes by the post-labeling assay. Whether these adducts contain trenbolone or not, they should be further characterized in order to make sure they do not pose a risk.

198. Concerning the set of studies "re: estradiol metabolism in cattle", Dr Boobis has well noticed the presence of estradiol-17-esters as tissular residues. Nevertheless, his comment does not integrate a possible different absorption route by the lymphatic circulation. This specific point has been demonstrated in the same set of studies in cannulated piglets. Concerning this specific class of estrogens, currently there is a gap in our knowledge of the extent to which they have some hormonal effect in peripheral tissue but also in intestine when ingested. Moreover, when considering the *in situ* catechol estrogens formation in target tissues of exposed consumers (in particular at the intestine level), there is still a gap about the complete residue information on the parent compound but also on the metabolites, specifically on estradiol-alpha. This latter compound gives the same DNA-adducts pattern from catechols as estradiol (Jouanin *et al*, Steroids 67 (2002), 1091-1099). This information is pivotal when considering the risk of genotoxicity of all estrogen residues, not only this of estradiol. It should be recalled that all residue data on tissular estrogen were obtained by a fully validated spectro-physical procedure, discarding any doubt on false positive signals. Such reference data were never obtained at this sensitivity and precision level with any other hormones considered before.

199. As regards the criticism of Dr. Boobis of the Chakravarti et al. study concerning in particular the comment that the two major adducts formed by E2-3,4-quinone are N3Ade and N7Gua, it should be noted that both adducts are spontaneously released from the DNA (a process called depurination) but at different rates (Zahid et al., 2006): the N3Ade is depurinated much faster than the N7Gua. Therefore, the N7Gua may allow accurate DNA repair whereas the N3Ade may not be repaired properly and give rise to mutations of the type observed in the mutagenicity studies. What is important to stress, however, is that Chakravarti et al (Oncogene, 20; 7945-7953, 2001) has detected mutations in the H-*ras* gene in the skin of SENCAR mice following dermal treatment with E2-3,4-quinone, with the specific nature of the mutations detected being consistent with the expected depurination of adenine due to the formation of an E2-3,4-quinone-Adenine adduct. This is relevant to the potential mutagenicity of estradiol in humans. First, we know that oxidative metabolism of E2 to the E2-3-4-quinone metabolite occurs in human breast tissue because E2-quinone adducts to glutathione have been detected (Yue et al. J. Steroid Biochem. Mol. Biol. 86: 477-486, 2003). Second, adducts of the E2-3,4-quinone with ademine and guanine have been detected in the mammary tissue of ACI rats injected into the mammary gland tissue with 4-OH E2 or E2-3,4-quinone (Carcinogenesis, 25:, 289-297, 2004). So, Dr. Boobis criticism appears to miss the important point that mutagenicity *in vivo* is now established thanks to this and the other studies cited by the European Communities in relation to Question 13 above.

200. It follows that Dr. Boobis provides a partial and selective discussion of certain aspects of these studies. The importance of these studies is however not questioned. If some of the results obtained by some of these studies are not clear or unequivocal, this simply strengthens the EC position that important gaps in our knowledge have become available recently which made the completion of a risk assessment impossible in 2000-2002 and even today for the five hormones (except for oestradiol 17β)

ANNEX F-4

COMMENTS BY THE UNITED STATES ON THE REPLIES OF THE SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC TO QUESTIONS POSED BY THE PANEL

(30 June 2006)

A. INTRODUCTION

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

B. THE ROLE OF SCIENTIFIC EXPERTS

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

C. COMMENTS ON THE EXPERTS' RESPONSES

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

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

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

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

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

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

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

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

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

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

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

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human health from hormone residues in bovine meat and meat products", 10 April 2002 ("2002 Opinion") (Exhibit US-1).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1. Risk assessment

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

(a) Risk assessment procedures generally

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

13. As noted by Codex, JECFA and Dr. Boobis, there are numerous international documents and guidance materials relevant to the assessment of veterinary drugs in food, dating back to at least 1987.[14] In addition, Dr. Boisseau comments that the assessment of such drugs has been "internationally harmonised through scientific conferences and it is possible to say there is an international non written agreement on this rationale."[15] As noted by JECFA, "[a]ll of these documents are the outcome of international expert meetings and represent the agreed views of the

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

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

[14] *See* Codex Responses to Questions from the Panel ("Codex Responses") (Questions 3 and 4), pp. 4-5; JECFA Responses to Questions from the Panel ("JECFA Responses") (Question 3), pp. 2-3; Responses to Questions from the Panel of Dr. Alan Boobis ("Dr. Boobis Responses") (Question 3), pp. 10-11.

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

participating experts and several of those have also been published in the scientific literature."[16] Although there are no Codex standards *per se* on the conduct of a risk assessment (such guidance is currently in draft form[17]), as noted by JECFA, "[t]he elaboration and application of risk assessment principles are within the responsibility of the scientific expert bodies [*i.e.*, JECFA]."[18]

14. In terms of the components comprising a risk assessment, the experts' responses confirm that there are four essential elements: (1) hazard identification; (2) hazard characterization; (3) exposure assessment; and (4) risk characterization.[19] The one caveat to this rule is provided by Dr. Vincent Cogliano, who notes that, for purposes of hazard characterization, "[a] qualitative risk assessment can consider the presence or absence of dose-response relationships."[20] JECFA's response takes this thought a step further, noting that a dose-response assessment is an integral part of hazard characterization, and can be "done in a quantitative or a qualitative way. In the qualitative sense this is the determination of a no-effect level from an experimental or epidemiological study. For the hormones JECFA used this approach."[21] The definition of "hazard characterization" provided by Codex confirms that a dose-response assessment is integral to this step of risk assessment.[22] The EC's Opinions fail to engage in any such evaluation because they rely instead on the conclusion that estradiol 17β is genotoxic; however, as discussed in greater detail below, and as confirmed by the scientific experts, the EC fails to adduce evidence of genotoxic or carcinogenic effects at levels below those associated with a hormonal response.

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

16. Dr. Boobis reiterates this point, noting that the results of JECFA's risk assessment are based on scientific evidence as opposed to a predetermined result, "JECFA['s] risk assessment concluded that the dose-response relationship for all of the endpoints was non-linear and that there was a threshold dose below which there was no appreciable risk over a lifetime of exposure. Hence, a deterministic approach, via the establishment of ADIs, was appropriate according to the procedures

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

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

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

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

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

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

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

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

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

followed by the Committee."[25] Finally, as noted by JECFA itself, "JECFA's assessment process is based on the mechanism of action of the compound to be evaluated, non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect. In such a case, as for the hormones, a no-effect level can be determined."[26]

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

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

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

19. The experts' responses confirm that, while the EC Opinions engage in hazard identification,[31] the first step of a risk assessment, the Opinions fail to complete any of the remaining three components (hazard characterization; exposure assessment; and risk characterization). Dr. Boobis notes, "[t]he EC has not identified the potential for adverse effects on human health of residues of oestradiol found in meat from treated cattle. This is because the analysis undertaken was focused primarily on hazard identification. There was little in the way of hazard characterization, and no independent exposure assessment was undertaken,"[32] indicating that the EC's Opinions "do[ ] not follow the four steps of the Codex risk assessment paradigm. Even if it were concluded that oestradiol is a genotoxic carcinogen, the four steps should have been followed."[33] In other words,

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

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

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

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

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

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

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

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

[33] Dr. Boobis Responses (Question 14), p. 18. Regarding the notion that residue levels found in meat from treated cattle cause genotoxic effects, Dr. Boisseau opines "the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans." Dr. Boisseau Responses (Question 13), p. 11.

"[t]here was no attempt to estimate the potential occurrence of adverse effects in humans following exposure to levels of hormones found in meat from treated animals."[34]

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

21. The experts' responses confirm that the EC's Opinions fail to engage in a dose-response assessment, which is part of the hazard characterization stage (the second step of risk assessment). Such an assessment would have been appropriate in the analysis of a hormone such as estradiol 17β for which a wealth of scientific evidence exists indicating that any effects caused by estradiol 17β are through the receptor-mediated (endocrine), cell division stimulating activity of the hormone, and not by genotoxic (non-endocrine) effects. Rather than evaluating this evidence in its Opinions, the EC relies instead on its assertion that estradiol 17β is genotoxic as an excuse for failing to conduct a dose-response assessment.[39] As noted by Dr. Boobis, it was improper for the EC to stop its assessment of estradiol 17β at this stage, "[f]or compounds that are known or assumed to be genotoxic via DNA reactivity, genotoxic potential would normally have to be confirmed in vivo before this endpoint would be used as the basis for a risk assessment."[40] As discussed in greater detail below, and as confirmed by the experts, the scientific studies cited by the EC fail to demonstrate this potential in vivo.[41]

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

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

[34] Dr. Boobis Responses (Question 13), p. 18.
[35] Dr. Guttenplan Responses (Question 13), p. 3.
[36] Dr. Guttenplan Responses (Question 14), p. 4.
[37] Dr. Guttenplan Responses (Question 14), p. 3.
[38] Dr. Boobis Responses (Question 12), p. 17.
[39] *See* Dr. Boobis Responses (Question 13), pp. 17-18.
[40] Dr. Boobis Responses (Question 36), p. 36, citing CVMP (2004). Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing; *see* Dr. Boisseau Responses (Question 36), p. 20 ("A dose-response assessment is not feasible for substances that are found to be genotoxic if ... this genotoxic potential can be expressed in in vivo conditions.")
[41] *See* Dr. Boobis Responses (Questions 16, 18, 20 and 52), pp. 19-20, 22, 23, and 44 (concluding that estradiol 17β is not genotoxic in vivo); Dr. Boisseau Responses (Question 13), pp. 9-11; *see* Section C(2)(b) below.

> endogenous production of some of these hormones by the animals and the human beings.[42]

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

23. Dr. Boisseau comments, "[t]he European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute [to such a risk]."[43] Dr. Boobis notes, "[t]he EC Opinions and other materials referred to by the EC do not quantify the extent to which residues of the hormones contribute to aggregate exposures or cumulative multiple hazards." Finally, Dr. Guttenplan opines, "[i]n general the EC do not attempt to evaluate 'the additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'."[44]

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

> [a]s soon as the [EC] accepts to consider[ ] these residues resulting from these therapeutic and zootechnical use[s] of oestradiol-17β as negligible [*i.e.*, by permitting their ongoing use for these purposes], it enters into a quantitative, or at least in a semi quantitative, exposure assessment procedure for these [ ] residues and, starting from that, it has no good reason to object to consider a wider exposure assessment covering all the residues resulting from the different sources of oestradiol-17β.[45]

Dr. Boobis comments, "[t]o my knowledge no account is taken of hormone treatments of cattle for purposes other than growth promotion, such as for therapeutic purposes, by the EC in its assessment of the aggregate or cumulative effects of the hormones in meat from cattle treated for growth promotion."[46] Dr. Guttenplan indicates that the EC's decision to except zootechnical or therapeutic treatments from its ban is "a reasonable response," yet he does not appear to address the Panel's inquiry, *i.e.*, whether the EC, in its Opinions, took these treatments into account in an assessment of cumulative effects.[47]

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

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

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

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

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

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

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

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

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

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

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

27. In addition to failing to complete the four steps for a risk assessment, the EC's Opinions also fail to properly address critical factors such as the bioavailability of estradiol 17β[54] and DNA repair mechanisms.[55] The experts' responses note that bioavailability relates to the oral route of exposure to hormone residues, a route that is "not the most efficient,"[56] and that the bioavailability of a substance, in this case estradiol 17β, "has to be taken into consideration in the risk assessment, in particular at the third step regarding the exposure assessment of residues."[57] Indeed, as a general rule "only that fraction of the dose that is bioavailable is toxicologically relevant."[58] The United States has argued that the EC has failed to take into account the low bioavailability of estradiol 17β in its assessment of that hormone, and none of the experts' responses appear to indicate otherwise.[59]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

estradiol 17β than previously thought; and (2) miscasts as "paradoxical" a US argument relating to bioavailability.

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

30. Dr. Guttenplan indicates that a conclusion reached by the United States (that bioavailability of estradiol 17β is low)[64] based in part on a EC study evaluating the metabolism of estradiol 17β is "paradoxical" to the results of the study because, according to Dr. Guttenplan, in the study "estradiol was converted to estrone, so it must have entered the cell."[65] It is true that estradiol was converted to estrone in the study; however, the focus of the US argument was the evaluation of whether or not estradiol 17β, the alleged "bad actor" implicated by the EC as a genotoxic carcinogen was transported across the single-cell layer (used to mimic the human intestinal wall in the study). Whether or not estradiol 17β entered the cells is irrelevant to the point made by the United States. Rather than being transported across the single-cell layer, all of the estradiol 17β that entered the cells was metabolized into estrone or other metabolites, which have been shown in studies cited by the EC to be benign in terms of genotoxic carcinogenicity.[66]

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

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

[64] *See* US Rebuttal Submission, para. 41. Note that the study's author confirms the US argument regarding bioavailability of estradiol 17β, concluding that the study's result "indicates that 17β-estradiol is not absorbed intact in the human intestinal tract." Hoogenboom, Investigations on the metabolism of 17β-estradiol by bovine hepatocytes, human intestinal and breast cells, and the genotoxic and estrogenic properties of the metabolites (unpublished), p. 5. (Exhibit EC-6 (US)).

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

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

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

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

[69] Dr. Guttenplan Responses (Question 22), p. 7. Dr. Guttenplan states that "since it [DNA repair] is not likely to be different for estrogen derived damage than other types of damage it is not really relevant." This statement requires clarification, as it would appear to the United States that DNA repair of estrogen-derived

(c) Conclusion

32. The experts' responses regarding the necessary components or elements of a risk assessment and their opinions as to whether or not the EC has satisfied each of those elements confirm that the EC has not conducted a risk assessment for estradiol 17β, the one hormone for which it claims to have done so.[70] Therefore, the EC has failed to base its permanent ban on meat and meat products from cattle treated with estradiol 17β on a risk assessment, as required by Article 5.1 and defined in Annex A, paragraph 4 of the SPS Agreement.

2. Scientific evidence relating to estradiol 17β

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

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

34. The experts' responses confirm that the scientific evidence cited by the EC in its Opinions does not support the conclusion that the carcinogenic effects of estradiol 17β are related to a mechanism other than hormonal activity. Dr. Boisseau notes, "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity."[72] Dr. Boobis concurs, "[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity."[73] One expert, Dr. Guttenplan, restates the conclusions of both parties, noting that while the EC has cited materials that "indicate that a mechanism other than hormonal activity is possible," the "United States and Canada cite other reports indicating that genotoxic effects of estrogens are unlikely."[74] While this

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damage is extremely important to an analysis of whether or not that specific form of damage is occurring, and the resulting likelihood of said damage.

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

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

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

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

[74] Dr. Guttenplan Responses (Question 16), p. 4. Rather than elaborating on how the EC's Opinions support the conclusion (*e.g.*, with scientific evidence) that the carcinogenic effects of the hormones at issue are

statement likely requires further clarification, the United States notes that additional responses from Dr. Guttenplan appear to indicate that he is of the opinion that any carcinogenic effects of estradiol 17β are indeed linked to hormonal activity or to levels greater than those found in residues in meat from cattle treated with hormones for growth promotion purposes. For example, Dr. Guttenplan concludes that any carcinogenic effect from estradiol 17β in meat from treated cattle "is unlikely if good veterinary practices are followed."[75]

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

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

36. Regarding the specific studies relied upon by the EC in reaching its conclusion that estradiol 17β is genotoxic, Dr. Boobis notes that the studies "should have been evaluated on a weight of evidence basis. Several of the studies suffered from significant limitations and there were a number of well conducted studies on a variety of endpoints that should have been included in such an evaluation."[78] Dr. Boobis provides numerous citations on the issue of genotoxicity and estradiol that were not considered by the EC in its Opinions, all of which have been published since 2000.[79] According to Dr. Boobis' analysis of the issue, none of the available evidence demonstrates that estradiol 17β is genotoxic in vivo.[80] The importance of this statement is underscored by the fact that the EC's own Committee for Medicinal Products for Veterinary Use ("CVMP") has a published guideline for evaluating the safety of residues of veterinary drugs in human food "requiring confirmation of an in vitro positive using an appropriate in vivo assay."[81] The EC has failed to explain why their evaluation of estradiol 17β is not subject to this guideline.

37. Dr. Boisseau notes that the EC provides "no data indicating that oestradiol-17β is associated with the increase of tumours in tissues or organs which are not hormone dependent," and that, "[i]n conclusion, the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans."[82] This comment by Dr. Boisseau is further emphasized by Dr. Boobis, who states, "the important point here is that it is the carcinogenic effect that is of concern, not in vitro genotoxicity."[83]

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related to a mechanism other than hormonal activity, Dr. Guttenplan simply recites the Opinions' conclusion that this is so.

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

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

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

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

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

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

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

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

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

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

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

40. Dr. Boobis agrees, stating, "[t]here is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this. Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance."[89] Dr. Cogliano concurs, noting that the EC's statement regarding the lack of a threshold has not been demonstrated by the scientific evidence.[90] Dr. Cogliano also opines that the US stance on thresholds has not been supported by the scientific evidence, but this opinion does not appear to be relevant to the evaluation at hand, which is whether or not the EC, in banning the import of meat from cattle treated with estradiol 17β for growth promotion purposes, adduces the necessary scientific evidence relating to, *inter alia*, genotoxic effects of the hormone, to serve as a basis for its ban.[91]

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

[84] Dr. Guttenplan Responses (Question 19), p. 5.
[85] Dr. Guttenplan Responses (Question 19), p. 5.
[86] Dr. Guttenplan Responses (Question 15), p. 4.
[87] *See* Panel's Questions to the Experts, Question 19.
[88] Dr. Boisseau Responses (Question 19), p. 16.
[89] Dr. Boobis Responses (Question 19), p. 22.
[90] Dr. Cogliano Responses (Question 19), p. 2.
[91] As noted in paragraph 39 above, Dr. Guttenplan's response appears to neither endorse or deny the presence of a threshold. His answer does appear to indicate, however, that it would have been possible for the EC to determine a safe level for estradiol 17β, or to have examined the effects of low doses, rather than simply stopping its evaluation once it concluded estradiol 17β is genotoxic. ("The statement that, 'the fact that doses used in growth promotion are low is not of relevance' is not necessarily true. For any toxin the dose determines the risk." "When exposure is very low risk will be very low." Carcinogenic effects are "unlikely if good veterinary practices are followed.") Dr. Guttenplan Responses (Questions 15 and 19), pp. 4-5.

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

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

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

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

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

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

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

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

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

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

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

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

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

43. Dr. Cogliano, while noting that the identification of estradiol 17β as a human carcinogen "indicates that there are potential adverse effects on human health"[103] when it is consumed in meat from treated cattle nevertheless also comments that "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans,"[104] a statement which appears to endorse the conclusion that the EC has failed to demonstrate that carcinogenic or genotoxic effects will be caused by estradiol 17β residues in meat from treated cattle.

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

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[98] Dr. Boisseau Responses (Question 15), p. 12.
[99] Dr. Boisseau Responses (Question 15), p. 12.
[100] The EC has presented no evidence, for any sector of the human population, that consumption of beef affects circulating (blood) levels of estradiol 17β.
[101] Dr. Boobis Responses (Question 15), p. 18.
[102] Dr. Guttenplan Responses (Question 15), p. 4.
[103] Dr. Cogliano Responses (Question 15), p. 1.
[104] Dr. Cogliano Responses (Question 18), p. 1.
[105] Dr. Boobis Responses (Question 17), p. 21.
[106] Dr. Boisseau Responses (Question 17), p. 14.
[107] Dr. Cogliano Responses (Question 17), p. 1.

(d) Conclusion

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

3. Scientific evidence relating to the five provisionally banned hormones

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

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

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

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

[108] *See* Panel Report, *Japan – Apples (21.5)*, paras. 8.145-8.146.
[109] Dr. Boobis Responses (Question 61), p. 49.
[110] Dr. Guttenplan Responses (Question 61), p. 13.

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

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

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

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

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

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

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

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

[115] *See* Dr. Boobis Responses (Question 62), pp. 49-58 ("There is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat from treated animals can be assessed. Whilst additional information has been obtained on a number of aspects of the hormones in question, this was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded on previous knowledge. The evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion.")

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

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

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

"[t]here is no conclusive evidence presented by the EC that the five hormones ... when consumed as residues in meat have genotoxic potential."[119]

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

51. The experts' responses confirm that the scientific materials produced and cited by the EC (including the "17 Studies") have not identified any substantial gaps or insufficiencies such that more study is necessary before the risk from consumption of meat from cattle treated with the five hormones for growth promotion purposes can be assessed. Dr. Boisseau notes, "[t]hese new [EC] data do not demonstrate any important gaps, insufficiencies and contradictions in the scientific information."[120] Dr. Boobis agrees: "[t]here is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat ... can be assessed."[121] Further, "[t]he evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion."[122]

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

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

[119] Dr. Guttenplan Responses (Question 21), p. 6.
[120] Dr. Boisseau Responses (Question 62), p. 28.
[121] Dr. Boobis Responses (Question 62), p. 58.
[122] Dr. Boobis Responses (Question 62), p. 58.
[123] *See* Dr. Guttenplan Responses (Question 62), p. 14. (Dr. Guttenplan identifies "gaps" in the following areas: estrogen levels in children; identification and quantification of lipoidal esters; and matched population studies comparing various populations of children).
[124] Further clarification would be necessary to determine whether Dr. Guttenplan was of the opinion that data "gaps" existed for any of the five provisionally-banned hormones.
[125] *See*, *e.g.*, EC First Written Submission, para. 17 ("[The EC's ban] is based on a comprehensive risk assessment and, thus, is fully compliant with the DSB recommendations and rulings. In particular, as stipulated by the Appellate Body, the results of the risk assessment 'sufficiently warrant' the definite import prohibition regarding one of the hormones (Article 5.1 of the SPS Agreement).")

not say that any of these alleged gaps prevented conducting a risk assessment for any of the hormones.

(d) Conclusion

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

4. Scientific evidence relating to the hormones generally

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

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

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

57. The experts' answers confirm that, while it is necessary to take into account the long latency period of cancer in evaluating the safety of the six hormones, each of the hormones has been used for growth promotion purposes in cattle and evaluated for a sufficient period with no evidence of adverse effects to consumers to adequately address this concern.[127] Dr. Boobis notes, "the latency period is an important consideration," but confirms that studies of animals and humans "cover[ ] a sufficiently long period to encompass the latency period for any carcinogenic effects of the hormones."[128]

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

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

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

Further, "[t]he long term studies of the hormones undertaken in experimental animals and in humans, involved much higher doses than would be encountered on consumption of meat from animals treated with growth promoting hormones."[129]

58. Dr. Boobis notes the difficulty in distinguishing results among effects from hormone residues in food, naturally-occurring hormones and other factors, but agrees that "the hormones in dispute have already been used as growth promoters over a sufficient number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters."[130] Dr. Guttenplan concurs that hormones have been consumed in meat for a "sufficient number of years to observe strong or moderate increases in risk."[131] Yet, as described in detail in the discussion of epidemiological studies and recent materials cited by the EC below, there is no evidence of such increases.

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

59. The experts' responses confirm that the epidemiological studies cited by the EC in its Opinions fail to identify a link between hormone residues in meat and cancer.[132] Dr. Guttenplan concludes, "[t]he epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters."[133] As noted by Dr. Boobis, "[t]here is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans."[134] Indeed, the correlation lies not between hormone residues and cancer, but instead the association with cancer "is strongest with meat consumption and show[s] little relationship with whether the meat is from animals treated with growth promoting hormones or not."[135]

60. Dr. Boisseau cites back to an earlier response in which he comments, "the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues from the treatment of cattle with growth promoters."[136] Dr. Cogliano agrees, stating that "[t]he difference between the US and the EC in rates of breast cancer and prostate cancer almost certainly has multiple causes," and that while it is "possible that differences in exposure to exogenous

[129] Dr. Boobis Responses (Question 23), p. 26.
[130] Dr. Boisseau Responses (Question 23), p. 17.
[131] Dr. Guttenplan Responses (Question 23), p. 7.
[132] Confounding factors play a role in the evaluation of epidemiological data. The experts are split as to whether these factors can be identified and their effects attributed to a particular source. *See* Dr. Boisseau Responses (Question 24), p. 17. However, there is agreement that such factors exist, and that they should be taken into account in the interpretation of data used in a risk assessment. *See* Dr. Boobis Responses (Question 24), p. 27; Dr. Cogliano Responses (Question 24), p. 2; Dr. Guttenplan Responses (Question 24), p. 9 ("These are important considerations for risk assessment of adverse affects caused by residues of growth promoting hormones in meat, as the effects of the hormones (if any) are likely to be small and might be obscured by confounders.") None of the experts express the opinion that the EC's Opinions took confounding factors into account in the assessment of the safety of the hormones.
[133] Dr. Guttenplan Responses (Question 26), p. 9. Dr. Guttenplan also notes that "[t]he references to the higher rates of breast cancer and prostate cancer observed in the United States as compared to the [EC] are not very convincing," and that "the differences in rates of breast cancer and prostate cancer ... are relatively small." Dr. Guttenplan Responses (Question 24), p. 9.
[134] Dr. Boobis Responses (Question 26), p. 32.
[135] Dr. Boobis Responses (Question 26), p. 32.
[136] Dr. Boisseau Responses (Question 26), p. 17, *citing* earlier responses on pp. 16-17.

hormones can be one cause, [ ] the data are not sufficiently specific to establish a link between these observations."[137]

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

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

63. The final expert, Dr. Cogliano, appears to support the conclusions of the other experts, noting that "[t]he study by Norat et al (2005) indicates a risk to human health from the consumption of meat."[145] As noted above, this conclusion is unexceptional, as it is not evidence of a risk from residues in meat from cattle treated with any of the six hormones for growth promotion purposes, but rather relates to meat consumption generally.[146] For example, as described in paragraph 59 above, Dr. Boobis agrees that the correlation between consumption of meat and any cancer risk lies not between hormone residues and cancer, but instead "is strongest with meat consumption and show little relationship with whether the meat is from animals treated with growth promoting hormones or not."[147] As for the remaining two studies, Dr. Cogliano concludes that the studies merely "suggest a risk to human health," and clarifies his response by noting that the word "suggest" is used instead of "indicates" because "the exposure levels in these studies are higher than those found in meat residues."[148]

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[137] Dr. Cogliano Responses (Question 26), p. 2.
[138] *See* Dr. Boobis Responses (Question 25), pp. 29-31.
[139] Dr. Guttenplan Responses (Question 25), p. 9.
[140] Dr. Guttenplan Responses (Question 25), p. 9.
[141] Dr. Guttenplan Responses (Question 25), p. 9.
[142] Dr. Boisseau Responses (Question 25), p. 17.
[143] *See* Dr. Boisseau Responses (Question 25), p. 17. Dr. Boisseau notes that the third study is out of his scope of expertise.
[144] Dr. Boisseau Responses (Question 25), p. 17.
[145] Dr. Cogliano Responses (Question 25), p. 2.
[146] *See* Dr. Boobis Responses (Question 26), p. 32.
[147] Dr. Boobis Responses (Question 26), p. 32.
[148] Dr. Cogliano Responses (Question 25), p. 2.

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

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

(i) The assay relied upon by the EC to demonstrate lower circulating estradiol 17β levels in children has not been validated

65. The experts' responses confirm that it is critical that assays be validated before they are used as the basis for conclusions in a risk assessment.[149] Yet, no evidence has been presented demonstrating that the assay for estradiol 17β relied on by the EC, the Klein assay,[150] has been properly validated since it was first used in 1994. As noted by Dr. Boobis, the original Klein assay (1994) "reported very low levels of oestradiol in male children ..., but in a later study (Klein et al, 1998), the same group reported mean levels somewhat higher, at 0.27 pg/ml. The reliability of the Klein et al assay has yet to be determined."[151] Dr. Boobis comments, "[t]he assay is particularly sensitive to oestradiol, but there is no obvious explanation for this, as it relies on the affinity for the oestrogen receptor."[152] When compared to other results from yeast-based assays, it is clear that "results with the yeast reporter assay are not consistent, and use of such data in risk assessment requires that the assay be adequately validated."[153]

66. An important step in assay validation is confirmation of the results reported by the original author(s) by scientists in another, independent laboratory. Dr. Sippell notes that the "validity of the [Klein assay] has now been confirmed by another [assay] of E2 [estradiol 17β] which was developed by Charles Sultan's group at the University of Montpellier, France (Paris et al 2002). Unfortunately, the complexity of the [assay] so far prevents its wider use for routine measurements in small serum samples from infants and prepubertal children."[154] However, the Klein assay and Paris assay cited by Dr. Sippell differ in significant ways, and it cannot be stated that the latter independently confirms the results of, or validates the former. For example, the two assays employ different media – the Klein

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

[150] The EC's own CVMP concludes the following regarding the Klein assay: "It was noted that the report by Klein et al. (1994) indicated much lower plasma levels of oestradiol when measured with a new method, based on -galactosidase gene expression in genetically modified yeast, compared to the classical RIA requirements (Klein et al., 1994). However, (i) the measure was made only in plasma and needs to be carried out in other tissue(s) to enable to comparison between the intake of residual oestradiol and the endogenous levels, [and] (ii) the methodology needs validation and is not (yet) generally accepted." CVMP (1999), *Report of the CVMP on the Safety Evaluation of Steroidal Sex Hormones in particular for 17β-Oestradiol, Progesterone, Altrenogest, Flugestone acetate and Norgestomet in the Light of New Data/Information made available by the European Commission* (EMEA/CVMP/885/99) ("1999 CVMP Report"). (Exhibit US-5). *See* 1999 EC Opinion, § 2.2.2.1 ("Physiological levels of steroids in serum during childhood and puberty"), p. 11; Table 1, p. 28. (Exhibit US-4).

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

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

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

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

assay utilizes yeast cells and the Paris assay mammalian cells (a human cancer cell line (HeLa cells)). In addition, the Paris assay reflects circulating levels of estradiol 17β at least an order of magnitude greater than those identified in the 1994 Klein assay.[155] In order to conclude that the work of Paris validated the assay relied on by the EC in its Opinions, there would have to be congruity in the results of the assays. Therefore, the EC has based conclusions in its Opinions on hormone levels in sensitive populations on an assay that has not been properly validated.

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

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

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

The materials cited by Dr. Sippell do not appear to be responsive to the Panel's question, which sought comment on the EC statement that "<u>any</u> excess exposure" to estradiol 17β <u>resulting from the consumption of meat</u> presents a potential risk to public health in particular sensitive populations such as prepubertal children. None of the citations made by Dr. Sippell address this specific question, nor do the studies cited by Dr. Sippell present any evidence that the low levels of estradiol 17β residues in beef (from either treated or untreated cattle) would be sufficient to affect the health or development of prepubertal children. Further, Dr. Sippell's responses appear to propose a different result than his own research, in which he has concluded "[a]lthough there is concern that oestrogen consumption through food might have adverse effects on pubertal development and human health, <u>there are no published data to support the notion that an increased overall exposure to environmental oestrogens has led to an increased incidence in precocious puberty or to an earlier start of pubertal development</u>."[161]

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

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

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

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

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

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

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

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

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

70. The Sun paper involved a large-scale study of sexual development in white, black and Mexican-American children in the United States. The study, which presents national reference data, concluded that non-hispanic black girls and boys had earlier ages for sexual maturity compared to the other two groups. The paper is limited to statistics on children in the United States and makes no effort to compare these data to those for European children. It is therefore unclear how Dr. Sippell reaches his conclusion that this phenomenon occurs "in particular in the USA and less in Europe."[162] In any event, the study does not examine or measure estradiol 17β at all, and therefore cannot be used as evidence in support of Dr. Sippell's conclusion that exposure to estradiol 17β results in "earlier sexual maturation in girls, in particular in the USA."[163] The Wu paper uses the same data set as the Sun paper, concluding that black and Mexican-American girls reach puberty at younger ages than white girls. As is the case with the Sun paper, Wu simply does not support the conclusions extrapolated from it by Dr. Sippell. Further, there is absolutely no evidence in either the Sun paper or the Wu paper to suggest that the observed differences in age of puberty may be attributable to the presence of estradiol 17β residues in meat.

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

72. The Teilmann article concludes that the prevalence of precocious puberty[164] in Denmark was very low (< 1 in 10,000); that it was higher in girls than in boys; and that the rate was constant

[162] Dr. Sippell Responses (Question 39), p. 1.
[163] Dr. Sippell Responses (Question 39), p. 1.
[164] In this study, precocious puberty was defined as onset of puberty before nine years of age in girls and ten years of age in boys.

between 1993 and 2001. However, the Teilmann study does not provide any evidence supporting Dr. Sippell's conclusion that high sensitivity to increased estradiol 17β levels results in higher incidences of precocious puberty in girls than in boys. The cause of precocious puberty is not only unknown, it was not even examined by the authors of the Teilmann paper.

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

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

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

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

[165] Felner and White, *Prepubertal gynecomastia: indirect exposure to estrogen cream*. Pediatrics 105 (2000), E55. (Emphasis added).
[166] Dr. Sippell Responses (Question 39), pp. 1-2.
[167] Tamoxifen is a drug which has been used in humans to treat breast cancer.
[168] Dr. Sippell Responses (Question 39), p. 2.

promotion purposes in cattle.[169] There is ample evidence in animal studies that, at levels of exposure greater than the levels found in meat residues from treated cattle, in utero exposure to estrogen can affect the development of the male fetus. However, it must be emphasized that this is only the case when exposure levels are orders of magnitude greater than those relevant to an analysis of residues in meat from cattle treated with hormones for growth promotion purposes.[170] Further, evidence for latent or delayed effects on adult reproductive function caused by exposure to hormones is limited at best and confounded by numerous other factors. Dr. Sippell appears to acknowledge this by noting that the evidence is (at best) "indirect."

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

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

79. Finally, in response to the Panel's inquiry of how risks for individuals arising from "hormones naturally present in meat differ from risks arising from the residues of hormone growth promoters," Dr. Sippell concludes that "[s]ynthetic hormone growth promoters such as Zeranol and its metabolites have been shown to be as potent as E2 and [DES] in increasing the expression of estrogen-related genes in human breast cancer cells (Leffers et al 2001). On the other hand, the synthetic androgen Trenbolone and gestagen Melengestrol bind with high affinity to the human androgen and progesterone receptors, respectively (Bauer et al 2000)."[173] No scientific evidence is cited by Dr. Sippell to support his conclusion that "[e]xposure during pregnancy might result in sever

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

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

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

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

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

transplacental virilisation of a female fetus."[174] Dr. Sippell's response appears to misconstrue the Panel's question, in that it discusses the hypothetical effects of synthetic hormones rather than discussing the differences in naturally-present hormone levels as compared to residue levels resulting from the use of hormones as growth promoters.

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

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

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

(iii) The materials cited by the EC do not place into doubt Codex conclusions on the safety of the hormones

83. The experts' responses confirm that the materials cited by the EC do not place into doubt Codex conclusions on the safety of the six hormones. Dr. Boobis opines that, even if circulating estradiol 17β levels in prepubertal children are lower than previously contemplated,[175] the JECFA ADI for estradiol 17β would still "appear to be appropriate for all groups of the population,"[176] including prepubertal children. Dr. Boobis notes that several intervening steps and factors must be considered in an assessment of any risk to this population: "this exposure is via the oral route, and bioavailability by this route is very low (<5%) (Fortherby 1996). In addition, very little of the

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

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

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

absorbed hormone will be free, over 95% being bound to plasma proteins such as SHBG. Such binding reduces the biological activity of the hormone (Teeguarden and Barton, 2004)."[177] Therefore, even if an assay indicates that circulating estradiol 17β levels are lower, reliance on this fact alone does not suffice to assess any potential risk.

84. Further, as has been discussed in detail in the experts' responses, JECFA has taken into account additional safety factors in order to adequately compensate for the lower circulating levels of hormones in sensitive populations such as prepubertal children. As noted by Dr. Boobis, JECFA employs a 10-fold safety factor to protect sensitive populations and another 10-fold adjustment for inter-individual variation.[178] In other words, "[i]n keeping with its risk assessment principles, the ADI established by JECFA would have been designed to protect all segments of the population, including prepubertal children."[179] Therefore the ADI for estradiol 17β has a 100-fold safety factor built in. Dr. Boisseau concurs that JECFA took into account sensitive populations in its risk assessments, and notes, "[f]rom a qualitative point of view, the risks for these individuals arising from residues resulting from the use of hormones as growth promoters in cattle does not differ from the risks arising from the residues of hormones naturally present in meat. The potential problem which may exist is only a quantitative one."[180]

85. According to Dr. Boisseau, this information was not taken into account by the EC in its purported risk assessment. He comments, "[t]his excess exposure of these sensitive populations needs to be assessed and compared with the exposure resulting from the daily consumption of meat from cattle which have not been treated by growth promoters, from other food and products of animal origin and from their own production of hormones."[181] Dr. Boobis concludes, "there is no requirement for any revision in the Codex recommendation with respect to oestradiol-17β on the basis of the material referred to by the EC."[182]

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

86. The experts' responses confirm that the scientific evidence cited by the EC fails to demonstrate adverse effects on the immune system or "other risks" to human health from the consumption of meat from cattle treated with the growth promoting hormones at issue. Dr. Boobis states, "[t]he evidence on immune effects of hormones such as oestradiol referred to by the EC does not identify any adverse effects on the immune system from consumption of meat from treated cattle. In general, clear evidence for immune effects were observed only at high doses."[183] He notes that

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

[178] Dr. Boobis Responses (Question 42), p. 39. Dr. Boisseau confirms that JECFA "has considered appropriate to establish a NOAEL on the basis of the changes in several hormone dependent parameters in post menopausal women and to derive from this NOAEL an ADI using two safety factors of 10, one to account for normal variation among individuals and a second one to protect the sensitive human populations." Dr. Boisseau Responses (Question 13), p. 9. Note that the EC's CVMP, in determining the estradiol 17β is safe for use for zootechnical and therapeutic purposes in cattle "based its risk assessment on the relation between any possible excess of hormones from zootechnically treated animals in the diet and the endogenous daily production of oestradiol in prepubertal boys." 1999 CVMP Report, p. 12. (Exhibit US-5). Dr. Sippell disagrees that JECFA has adequately taken into account sensitive populations, but it is unclear from his response if he is familiar with JECFA's safety factors or whether/why he finds these factors to be inadequate. Dr. Sippell Responses (Question 42), p. 3.

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

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

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

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

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

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

(e) Conclusion

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

5. Scientific evidence relating to residues

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

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

[184] Dr. Boobis Responses (Question 59), p. 48.
[185] Dr. Guttenplan Responses (Question 59), p. 13.
[186] Dr. Boisseau Responses (Question 59), p. 27.

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

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

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

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

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

92. However, as noted by Dr. Boisseau, older data is neither irrelevant or "bad" data simply due to its age. Rather, it is the quality and quantity of data that is important,[192] and for the hormones at issue, a great deal of high quality data exists.[193] Further, the MRL for a veterinary drug is the

[187] Dr. Boisseau Responses (Question 29), p. 18.
[188] Dr. Boisseau Responses (Question 29), p. 18.
[189] Dr. Boobis Responses (Question 30), p. 33.
[190] Dr. Boobis Responses (Question 62), pp. 50-52. *See* Section C(6) below for a detailed discussion of the misuse studies.
[191] Dr. De Brabander Responses (Question 29), p. 3.
[192] *See* Dr. Boisseau Responses (Question 34), p. 19 ("the quality and the number of the available data are more important than the dates at which these data have been produced.")
[193] As explained in JECFA's Responses (at pp. 7-9), JECFA has specific and extensive requirements for the residue data that are used to derive MRLs. These requirements include information on the analytical method

maximum concentration of residue that is legally permitted or recognized as acceptable, based on the toxicological hazard for human health (expressed as the ADI).[194] Therefore, the statement by Dr. De Brabander that the MRLs for the hormones "are high in relation to modern analytical limits" is unexceptional; in fact, by definition the MRL for a drug residue should be higher than the analytical limit of detection.[195]

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

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

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

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

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used to measure each residue and the performance factors of the method. Importantly, when comparing the 1988 and 1999 evaluations of residue studies for the hormones JECFA states, "[m]ost of the studies were the same. However, a few additional investigative studies were also reviewed. JECFA also performed a more detailed thorough review of the validity of the analytical methods used in the studies and only used data generated using valid methods." Therefore, Dr. De Brabander's statement that "from an analytical point of view these MRLs are unacceptable" is unfounded.

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

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

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

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

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

95. Dr. De Brabander also provides anecdotal information relating to a testosterone sex spray as well as use of a substance called "ZMA" (a substance allegedly used by athletes) in his response. However, none of this information is responsive to the Panel's question, nor does it provide evidence relating to hormone residue levels in meat from cattle treated with any of the six hormones for growth promotion purposes. For instance, the discussion of the androstenone (boar pheromone) spray neither provides any information regarding dose levels, nor is it relevant to the pathway at issue in the consumption of hormone residues in meat (*i.e.*, oral). ZMA is not one of the hormones at issue in this dispute, and the anecdotal discussion of its use by athletes does not appear to be relevant to a discussion of residues in meat from cattle treated with any of the six hormones for growth promotion purposes.

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

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

97. The experts' responses confirm that JECFA's recent re-evaluation of the three naturally-occurring hormones reached the same conclusion as earlier evaluations, *i.e.*, that residues of the hormones in meat from cattle treated for growth promotion purposes are safe for consumers. The EC argues that JECFA's establishment of ADIs for the three natural hormones at its 52nd Meeting in 1999 marked a shift in its thinking regarding the safety of the hormones when used as growth promoters in meat.[201] The experts indicate that it did not. Dr. Boisseau notes "[i]f the wording of the conclusions adopted by JECFA has been formally different, the substance of these conclusions remains unchanged," and that "[e]stablishing such ADIs had no specific implications as no MRLs have been established."[202] Further, "[t]hese new recommendations have not been considered by CCRVDF

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

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

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

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

because CCRVDF did not request JECFA to reassess these hormones and because the new proposals of JECFA did not change the substance of the previous ones."[203]

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

99. Dr. De Brabander is the lone expert to disagree with these conclusions, noting that JECFA's conclusion to set an ADI "is a recognition of the danger of hormones to human health and welfare in all of his [*sic*] aspects."[208] Dr. De Brabander does not provide any support for this statement, and does not clarify whether the "danger to human health ... in all of [its] aspects" includes levels of the hormones found in residues in meat from cattle treated for growth promotion purposes. The responses of JECFA, Codex and the other two experts indicate that the decision to set an ADI is not evidence of such a danger.[209] Rather, the setting of an ADI permitted an evaluation of residue levels of the three hormones that could be ingested without any danger or risk to consumers.[210]

(c) Conclusion

100. The experts' responses indicate that the EC has failed to put forward any scientific evidence demonstrating that residues of any of the six hormones in meat are greater than previously thought, or

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

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

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

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

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

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

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

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

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

6. Scientific evidence relating to good veterinary practices

101. The scientific evidence relating to good veterinary practices is relevant to the obligation in Article 5.1 of the SPS Agreement that Members must base their measures on a risk assessment, as appropriate to the circumstances, as well as Article 5.2's requirement that risk assessments take into account relevant processes and production methods, and relevant inspection, sampling and testing methods.[211] Further, an analysis of good veterinary practices is relevant to Article 5.7 of the SPS Agreement and an analysis of whether the EC's provisional ban is based on available pertinent information. The issue of conditions of use is, however, perhaps best understood in the context of Article 5.6 of the SPS Agreement, which provides that a Member must ensure that its sanitary and phytosanitary measures are not more trade-restrictive than required to achieve its appropriate level of sanitary or phytosanitary protection. The fact that the EC has raised the issue of misuse[212] and devoted considerable resources to demonstrating the potential consequences of misuse implies that it

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[211] For purposes of evaluation of SPS measures under the SPS Agreement, the Appellate Body stated, "[w]e must stress ... that Article 5 and Annex A of the SPS Agreement speak of 'risk assessment' only and *that the term 'risk management' is not to be found either in Article 5 or in any other provision of the SPS Agreement*." Further, the Appellate Body concluded that misuse and the analysis of the potential for failure of controls are topics that are included in a "risk assessment" for purposes of the SPS Agreement:

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

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

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

already recognizes that there are conditions under which residues of the six hormones used for growth promotion are safe. The only health question then would be whether there are particular conditions of use under which there would be a health risk. If so, then the question becomes whether the EC's sanitary measures are more trade-restrictive than required to achieve the appropriate level of protection from that risk within the meaning of Article 5.6 of the SPS Agreement.

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

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

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

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

105. As explained by the United States in its Rebuttal Submission, the US system of controls is not a simple matter of audits and paper work.[216] The United States, through cooperation between the Food Safety and Inspection Service ("FSIS") of the United States Department of Agriculture

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

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

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

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

("USDA") and the FDA, has rigorous programs in place which provide efficient safeguards against the hypothetical failure of controls in the production of meat and meat products. These programs include setting safe levels for veterinary drugs; monitoring for violative residues; and inspection of meat at the ante mortem, post mortem and processing stages. As large commercial operations, US feedlots have great incentive to comply with the regulations set and enforced by USDA and the FDA. In addition to regulation at the federal level, many states and even individual feedlots have Beef Quality Assurance Programs which set high standards for beef management practices to maximize the quality and safety of beef.[217] Key components of these programs include proper training of feedlot employees and managers to ensure that management practices do not lead to violative residues or quality defects.

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

107. Dr. De Brabander cites to two pieces of evidence in support of his conclusion that the US system of controls does not work or is subject to failure, neither of which appears to be convincing or germane to the debate of whether or not the EC has indeed evaluated the likelihood of this occurrence. He notes that "[t]wo years ago we had some american students in veterinary medicine in an exchange program; their knowledge of 'hormones' their use in the USA and the risks involved was almost zero."[219] At best this statement is anecdotal evidence, and it certainly cannot be extrapolated to the broader conclusion that controls are likely to fail in the United States. Dr. De Brabander also cites to a controlled study conducted by scientists at the University of California-Davis using Zilpaterol (a beta-agonist not approved by the FDA for commercial use in the United States) and Revalor (trade name for an FDA-approved growth promoting implant containing estradiol 17β and trenbolone acetate) in cattle as evidence "illustrat[ing] that farmers (and vets) have indeed economic incentives to misuse growth promoting substances."[220] The Zilpaterol study does not support this conclusion, nor does it document or endorse the commercial use of Zilpaterol. Rather, it is simply an example of a single research study, conducted under controlled conditions on a limited number of animals, in which scientists investigated the combined effects of two treatments on growth performance in cattle. Nothing in the Zilpaterol study speaks to the potential of failure of controls or misuse of growth promoting hormones in the United States.[221]

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

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

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

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

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

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

108. The experts' responses confirm that the material put forward by the EC regarding misuse or abuse of any of the six hormones fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes. Dr. Boisseau reiterates that JECFA does not perform an evaluation of the potential for misuse,[222] and notes that "the [EC] did not conduct a quantitative risk assessment from growth promoters, [and that] it is not possible to say the scientific evidence referred to by the [EC] assesses the risk to human health from residues resulting from these misuses/abuses."[223]

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

> 1. Lange *et al., Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: effect of the implant preparations Filaplix-H, Raglo, Synovex-H and Synovex Plus.*
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> "In study 5, the impact of misuse and multiple dosing on residual hormone levels in meat was determined. Dosing at up to 10 times the approved dose, resulted in an increase in the tissue concentrations of some hormones in some tissues to value above the MRL for those hormones for which Codex has established an MRL."[226]
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> "'Treatment with zeranol and testosterone propionate, even after multiple application, does not cause any problems, as far as infringement of threshold levels is concerned.'"[227]
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> "For oestradiol, the maximum increase observed in any tissue was not greater than proportional to the dose applied. Hence, even at 10-fold the approved dose, intake would be well below the ADI. This would be offset by the fact that not all tissues had such elevated levels, and the probability of consuming such high residue levels of a

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

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

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

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

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

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

regular basis is minimal. It should also be noted that Codex did not specify an MRL for oestradiol, as it was considered unnecessary."[228]

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

"In the study on misplaced implantation sites (Daxenberger et al, 2000), substantial residual hormone was sometimes found at the implantation site when this was not as recommended. However, for these findings to have significance for the consumer a number of factors need to be considered. These include the likelihood of off-label use of the hormones, the failure to detect the implantation site, the use of the implantation site for food use, the contribution of the contaminated meat to the diet and the frequency of such contamination. No data have been presented on the prevalence of such significant contamination as a consequence of the veterinary use of the hormones. Indeed, no evidence is presented that such misuse does occur with the consequences suggested by the authors."[229]

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

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

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

There is little information in the scientific studies initiated by the EC since 1997 that support the contention that they have identified important new gaps, insufficiencies and contradictions in the scientific information and knowledge on the hormones, and that additional studies are necessary before the risks to health of consumption of meat from treated animals can be assessed. Whilst additional information has been obtained on a number of aspects of the hormones in question, this was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded on previous knowledge. The evidence obtained did not indicate any additional concern regarding the risk from exposure to residues of the hormones in meat from cattle treated for growth promotion.[231]

111. Dr. De Brabander disagrees, noting that the materials put forward by the EC "call[ ] indeed into question" the applicability of Codex standards. However, Dr. De Brabander presents no scientific evidence in support of this conclusion. Dr. De Brabander cites to the "older" experiments

[228] Dr. Boobis Responses (Question 62), p. 50. (Emphasis added).
[229] Dr. Boobis Responses (Question 62), pp. 50-51. (Emphasis added).
[230] Dr. Boobis Responses (Question 62), p. 51. (Emphasis added).
[231] Dr. Boobis Responses (Question 62), p. 58. (Emphasis added).

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

(c) Conclusion

112. The experts' responses, insofar as they are based on the scientific evidence relating to good veterinary practices and misuse, confirm that the EC has failed to demonstrate that there is a risk to human health from the misuse of growth promoting hormones in the United States and that the material put forward by the EC regarding misuse or abuse of the hormones at issue fails to call into question Codex standards regarding the safety of meat from cattle treated with hormones for growth promotion purposes. Therefore, the experts' responses demonstrate that the EC has failed to base its import ban on meat from cattle treated with estradiol 17β on a risk assessment, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement, and has similarly failed to satisfy Article 5.2's requirement that a risk assessment take into account relevant processes and production methods and relevant inspection, sampling and testing methods. In addition, the experts' responses demonstrate that the EC has not satisfied its obligation under Article 5.7 of the SPS Agreement to base a provisional ban on available pertinent information. Finally, the experts' responses confirm that the EC, by imposing an import ban (whether permanent or temporary) on imports of meat from cattle treated with hormones for growth promotion purposes has breached its obligation to ensure that its sanitary and phytosanitary measures are not more trade-restrictive than required to achieve its appropriate level of sanitary or phytosanitary protection within the meaning of Article 5.6 of the SPS Agreement.

D. CONCLUSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ANNEX F-5

COMMENTS BY THE UNITED STATES TO THE COMMENTS BY THE EUROPEAN COMMUNITIES ON THE REPLIES OF THE SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC TO QUESTIONS POSED BY THE PANEL

(12 July 2006)

A. INTRODUCTION

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

B. GENERAL COMMENTS

1. Qualifications of experts

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

3. In addition to seeking to dismiss expert opinions based on an alleged lack of qualification, the EC also attempts to discard Dr. Boisseau's responses to certain questions based on the fact that he initially informed the Panel that he may not be in a position to respond to those questions. The fact that Dr. Boisseau was unsure as to his ability to respond to certain questions is not a valid reason for ignoring his ultimate responses to these questions. Indeed, Dr. Boisseau's responses appear to be very well-researched, and he has clearly put a great deal of effort into providing the Panel sound advice on these issues. Further, the United States notes that this is another example of the EC attempting to impugn the qualifications of an expert only where that expert has offered answers or points of view that do not support the EC's arguments. For example, the EC does not raise similar concerns regarding Dr. De Brabander's responses to Panel Questions 44-48 and 50-51 despite the fact that Dr. De Brabander, in an April 24, 2006 e-mail to the Panel noted, "I am an analytical chemist so I could only provide adequate answers to questions on residue analysis. That means Db question

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

[2]7-35 and f question 49."[2] Despite this statement delimiting his experience to residue analysis, Dr. De Brabander offers several responses on an entirely unrelated category: good veterinary practices in the United States and Canada.

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

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

5. In addition to confusing the role of experts in offering scientific advice to the Panel, the EC also notes in its comments that several of the Panel's questions concern aspects of risk assessment that are "not legally binding" since they are not referenced in the text of the SPS Agreement.[5] The EC appears to propose a very broad definition of what constitutes a risk assessment within the meaning of Article 5.1 of the SPS Agreement. Rather than accepting that guidance from international organizations such as JECFA and Codex provides important benchmarks for conducting a risk assessment and for objectively evaluating whether a Member's risk assessment has engaged in an adequate analysis of a risk, the EC instead proposes a notion of risk assessment devoid of any apparent form. The EC's concept of what is or is not a risk assessment ignores the text of Article 5.1, which states:

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

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

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

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

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

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

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

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

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

exposure assessment, and (iv) risk characterization."[9] The EC reiterates this conventional four-step risk assessment procedure in its 1999 Opinion.[10]

7. The EC further attempts to blur the notion of what constitutes an appropriate risk assessment for purposes of the SPS Agreement by repeatedly noting that the Appellate Body has concluded that risk assessments may be either quantitative or qualitative. However, the EC's description of the Appellate Body's conclusions is overly simplistic. Rather than finding, as the EC appears to argue, that Members may simply conduct a qualitative risk assessment that is devoid of any structure, necessary form or scientific rigor,[11] the Appellate Body simply determined that there is no requirement that a risk assessment establish a minimum quantifiable magnitude or threshold level of degree of risk.[12]

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

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

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

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[9] Panel Report, para. 8.103.

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

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

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

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

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

C. SPECIFIC COMMENTS ON EXPERTS' RESPONSES

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

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

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

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

14. The CVMP concluded that new risk assessments for estradiol 17β and progesterone were not necessary and that certain residue levels of the hormones are safe based on some very basic conclusions on these hormones (*e.g.*, lack of genotoxicity, carcinogenic action only after prolonged

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

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

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

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

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

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

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

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

exposure at high exposure levels) which contradict fundamental – but unsupported – conclusions set out in the EC's Opinions. It should be emphasized that the basic scientific information considered by the CVMP with respect to the risks of therapeutic and zootechnical use of hormones was the same information used by the SCVPH to assess the risks of hormones used for growth promotion, but the CVMP and SCVPH reached very different conclusions. Thus the CVMP evaluation is indeed relevant to this dispute and an analysis of the EC's Opinions, despite the EC's attempts to distance itself from the evaluation.[23]

15. Question 4: The EC dismisses the responses of two of the scientific experts (Drs. Boisseau and Boobis) and the international organizations by arguing that their responses are not limited to "legally binding" assessment techniques within the meaning of the SPS Agreement.[24] As noted above, it is not appropriate for the experts to comment on the legal nature of any aspect of the dispute. Further, the EC simply avers that the relevant guidelines or principles cited by the experts are not "legally binding" for purposes of analysis of a measure under the SPS Agreement, without providing an explanation of why this is so. Contrary to the EC's suggestion, the responses of Drs. Boisseau and Boobis, JECFA and Codex indicate that there are in fact "risk assessment techniques developed by the relevant international organizations" within the meaning of Article 5.1 of the SPS Agreement that are pertinent to an analysis of the EC's Opinions, in particular to an analysis of whether the EC has conducted a risk assessment for the permanently-banned hormone, estradiol 17β.[25] Indeed, the EC itself has recognized this fact.[26] In addition, the EC provides no explanation to support its allegation that its risk analysis techniques are "much more advanced than JECFA" nor does it explain what relevance, if any, this conclusion has to these proceedings.

16. Question 5: The EC claims that the experts' responses "do not take into account the legal requirements of the SPS Agreement." As noted above, it is not appropriate for the experts to comment on the legal nature of any aspect of the dispute. In addition, the EC attempts to contradict

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

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

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

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

the experts' responses with its own opinion, which appears to be of little relevance to the Panel's question, of how Codex and JECFA interact but provides no evidence to support this opinion.[27]

17. Question 6: The EC dismisses the responses of the scientific experts and international organizations by arguing that these responses are not limited to "legally binding" risk assessment techniques within the meaning of the SPS Agreement.[28] The EC simply avers that the relevant guidelines or principles cited by the experts are not "legally binding" for purposes of analysis of a measure under the SPS Agreement, without providing an explanation of why this is so other than an inapt citation to the *Hormones* Appellate Body Report discussing the distinction between "risk assessment" and "risk management." Contrary to the EC's suggestion, the experts (Drs. Boisseau, Boobis and Guttenplan) and JECFA confirm that there are four internationally-recognized steps to a risk assessment (hazard identification; hazard characterization; exposure assessment; risk characterization) and that these steps are in fact "risk assessment techniques developed by the relevant international organizations" within the meaning of Article 5.1 of the SPS Agreement that are pertinent to an analysis of the EC's Opinions, in particular to an analysis of whether the EC has conducted a risk assessment for the permanently-banned hormone, estradiol 17β.[29] In addition, the EC's comments appear to ignore the several conditions imposed on risk assessments by, *e.g.*, Articles 5.2 and 5.3 of the SPS Agreement.

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

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

20. The EC cites to a study by Bhat *et al*. (not cited in the EC's Opinions) as demonstrating "the necessary role of catechols of estradiol ... in induction of oxidative stress to induce tumors."

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

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

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

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

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

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

22. Question 8: The EC contrasts the experts' advice against its own unsupported scientific conclusions. For instance, the EC complains that "the evidence used by JECFA in the evaluation of these hormones is too old (dating from the 1970s) and has been obtained with outdated detection methods [*sic*] to be relevant today." This blanket conclusion is simply incorrect. For instance, JECFA based its conclusion to set ADIs for estradiol 17β, progesterone and testosterone on "[s]ufficient new data from observations in humans ... which were suitable to derive ADIs."[33] Further, the EC's argument presumes that older data is bad or incorrect data. As we have learned from the

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

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

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

experts' responses, this is not the case, but rather it is the quality and quantity of data that is essential.[34]

23. The EC argues that "JECFA did not take the low endogenous levels and thus the high sensitivity of children into account." Again, this conclusion is incorrect. As noted by the experts, JECFA did in fact take sensitive populations into account in its use of safety factors.[35] The EC also opines that use of hormones in oral contraceptives and hormone replacement therapy "demonstrates that estradiol and progesterone are bioavailable through the oral route." It is true that estradiol 17β and progesterone are administered orally for some indications. However, because their bioavailability is so low, very high doses are required to elicit the desired therapeutic effect. For example, therapeutic doses of estradiol 17β for oral administration range from 0.5 - 4.0 milligrams,[36] or 10,000 - 40,000 times higher than the 50 ng. derived from eating beef from cattle treated with estradiol 17β for growth promotion purposes. In addition to high doses, orally administered estradiol 17β and progesterone are also manufactured as micronized formulations (particle size < 10 microns) to further increase bioavailability. Even after micronization, the bioavailability of a 2 mg dose of estradiol 17β is still only about 5%. Lastly, synthetic estrogens used in these treatments have significantly higher oral bioavailability compared to the residues of the natural hormone estradiol 17β in meat from treated cattle.[37]

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

25. Further, the experts have confirmed that the decision by JECFA to set ADIs for the hormones in 1999 did not mark a change in its conclusion regarding the safety of the natural hormones. In short, as noted in the US Comments, the experts have confirmed that JECFA will only allocate an ADI for a food additive or veterinary drug if the scientific database is complete, unless it can adopt default assumptions that would if anything lead to a more conservative risk assessment than would be the case otherwise.[38] That database was sufficiently complete for the six hormones at issue in this dispute. The EC's failure to support its conclusions with the scientific evidence it relied upon in its

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

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

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

[37] For example, the bioavailability of ethinyl estradiol - the synthetic estrogen contained in combination oral contraceptives - is 55%. Fotherby K. Bioavailability of orally administered sex steroids used in oral contraception and hormone replacement therapy. Contraception 1996; 54: 59-69 (cited by Dr. Boobis in his responses to Questions 20 and 40).This is the reason why, e.g., oral contraceptives are not made from estradiol 17ß, but instead contain a synthetic estrogen (ethinyl estradiol) which is much more orally-bioavailable than estradiol 17ß.

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

Opinions demonstrates that those Opinions are not risk assessments, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement. Nor do the Opinions provide "available pertinent information" for a provisional measure within the meaning of Article 5.7 of the SPS Agreement.

26. Question 10: The EC argues that JECFA has a narrow mandate because it has not examined the likelihood of misuse or abuse of the hormones. As noted by the United States in its comments on the experts' responses, it would be extremely difficult for regulatory or standard-setting bodies to develop international food safety standards based on the assumption of misuse. Any veterinary drug can be misused, and if regulatory authorities base their evaluations against a misuse standard, then there would be virtually no approvals of veterinary medicines. A large number of veterinary drugs marketed around the world have been approved assuming that they would be administered according to good veterinary practices, indicating that this is the norm for such evaluations. It is therefore curious that the EC has not used this standard in its evaluation of the six hormones at issue in this dispute, assuming instead extreme misuse scenarios for each hormone.[39]

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

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

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

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

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

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

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

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

31. The EC also cites to the 2002 US Report on Carcinogens as "contradict[ing] the allegations made by the United States ... in these proceedings, which appears [*sic*] to be supported by Dr. Boobis, that the additional burden of residues coming from eating hormone-treated meat is so small that it would make no difference, compared to the level of endogenous production." Contrary to the EC's claim, in this dispute the US has accepted that concentrations of estradiol 17β may be slightly higher in edible tissues following treatment of cattle with estradiol 17β to promote growth.[44] The United States has simply argued, and demonstrated with evidence, that residue levels of hormones in meat from treated cattle would be within the physiological range of residue levels in meat from untreated cattle.[45] This position is entirely consistent with the statement quoted by the EC from the 2002 Report on Carcinogens.

32. The more complicated question posed to the experts was whether these marginally increased amounts of estradiol 17β are sufficient to elicit effects in the human consumer. As noted in the US

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

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

[44] *See* US First Written Submission, para. 51 ("Further, concentrations of estradiol 17β in meat from treated cattle do not vary significantly from concentrations in untreated cattle, *i.e.*, residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle. While tissue concentrations of estradiol 17β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels.") (Emphasis added).

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

Rebuttal Submission, the 2002 Report on Carcinogens indicates that they are not, concluding, "[t]he evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor", in other words, by the much higher concentrations of estrogens necessary to elicit a hormonal effect. Not, as the EC appears to insinuate, by concentrations found in meat products from cattle treated with hormones for growth promotion purposes.[46]

33. As noted by the United States in its Rebuttal Submission, the Report on Carcinogens' conclusion that estrogens are "known to be human carcinogens"[47] is unexceptional when applied to estrogens generally, as it is in the cited Report.[48] As noted in the US First Written Submission, there have been a number of epidemiological tests focused on women and the use of hormone replacement therapies and oral contraception, both of which contain estrogens.[49] The Report on Carcinogens takes these studies into account in its analysis, as well as the conclusions of the 1999 Report of the International Agency for Research on Cancer ("IARC").[50] JECFA took these same studies into account in 1999, noting the "[e]pidemiological studies on women who took estrogens alone or in combination with progesterone and androgens, showed that the risks for cancers at most sites were unaffected; however, the risks for cancers of the endometrium and breast were increased."[51] However, it attributed these effects to the "hormonal effects of estrogens", *i.e.*, to levels of estradiol 17β or other estrogens high enough to have a hormonal effect on the consumer.[52] This is one of the reasons that JECFA determined that levels of estradiol 17β found in meat from cattle treated with the hormone for growth promotion purposes according to good veterinary practices (levels exponentially lower than those causing hormonal effects) are safe.

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

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

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

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

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

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

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

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

[53] 1999 CVMP Report, pp. 8-9 (Exhibit US-5), citing the 52nd JECFA Report and the 1999 Report of the International Agency for Research on Cancer. (Emphasis added). *See also* 2005 U.K. Report, § 1.5.1,

have cited to IARC in support of the conclusion that any effects of estradiol 17β would result from levels of the hormone causing hormonal effects, rather than the exponentially smaller amounts found in residues in meat from treated cattle.

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

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

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

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

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("Overwhelming evidence suggests that sex steroids exert effects that are dose-dependent and that a threshold dose exists, below which, no biological effect will occur.") (Exhibit US-20).

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

[55] Exhibit EC-78.

[56] Exhibit EC-51C.

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

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

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

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

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

41. In Takahashi *et al.*, adenocarcinomas were induced in mice exposed subcutaneously to low doses of estradiol 17β in conjunction with intrauterine administration of the chemical carcinogen ENU. As explained in paragraphs 73 and 78 of the US Comments on the Experts' Responses, the subcutaneous (injected into the animal) route of estradiol 17β administration is not relevant to oral ingestion of estradiol in beef (how beef is actually consumed) because it bypasses the extensive first-pass metabolism in the intestine and liver which accompany oral ingestion or consumption of beef. Therefore, the relevance of the Takahashi study to potential effects of estradiol 17β in beef is questionable.

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

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[59] Dr. Guttenplan Responses (Question 14), p. 4.
[60] Dr. Guttenplan Responses (Question 15), p. 4.
[61] Dr. Guttenplan Responses (Question 14), p. 3.
[62] ERKO/Wnt-1 mice are genetically engineered to lack expression of estrogen receptor α.
[63] Exhibit EC-100.

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

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

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

46. Question 15: The EC notes, for Dr. Guttenplan's "benefit" that the Appellate Body has interpreted "potential" to mean "possible." It is not clear that this clarification is necessary, however, as Dr. Guttenplan already assumed that "[i]f potential is taken to mean possible" adverse effects are "unlikely if good veterinary practices are followed." As for Drs. Boobis and Boisseau, the EC attempts to dismiss their responses by noting that their opinions are "conditioned by their understanding that oestradiol-17β is causing cancer only through receptor meditated processes," a position that, according to the EC "is however scientifically no longer tenable in light of more recent evidence cited by the European Communities." The United States notes that the responses of Dr. Boobis and Dr. Boisseau are premised on a review of the very same evidence referred to by the EC. Drs. Boisseau and Boobis determined, upon review of that evidence, that their understanding is that oestradiol-17β causes cancer only through receptor mediated processes and that the EC has failed to present any evidence that would cause them to conclude otherwise. The EC comments that if the Panel "read[s] between the lines" of Dr. Boobis' and Dr. Boisseau's responses, it will note that they "do not seem to deny completely the existence of possible adverse effects." The EC provides no evidence in support of this conjecture.

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

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

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

conclusion that the EC has failed to demonstrate that carcinogenic or genotoxic effects will be caused by estradiol 17β residues in meat from treated cattle.[66]

48. Question 16: As noted above, the EC attempts to dismiss the opinion of Dr. Boisseau by noting that he has relied on the conclusions of JECFA, which the EC views as outdated, and has ignored the "more recent evidence" cited by the EC "showing the direct genotoxic potential of oestradiol 17β, progesterone, zeranol and most probable [*sic*] testosterone." As demonstrated by the United States and confirmed by the experts' responses, the EC has not shown these effects.[67] Therefore, it is perfectly reasonable for Dr. Boisseau to rely on JECFA's conclusions regarding the hormones. Regarding MGA and trenbolone acetate, the EC notes that "the evidence may be inconclusive but there are sufficient indications to treat them as such [genotoxic], despite the serious gaps in our scientific knowledge." However, the experts' responses have confirmed that these hormones are not genotoxic[68] and that there are not "serious gaps" in the scientific knowledge relating to MGA and trenbolone acetate.[69] Indeed, results of one of the EC's own "17 Studies" indicate that MGA was devoid of genotoxic activity, and that trenbolone and zeranol are non-genotoxic except at very high, cytotoxic (*i.e.*, high enough to kill the cell) concentrations.[70]

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

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

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

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

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

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

[70] *See* Exhibit EC-8.

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

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

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

appear to demonstrate that he is not, in fact, of the mind that levels of residues in meat from cattle treated with hormones for growth promotion purposes would be carcinogenic.

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

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

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

54. The EC notes that "more worrying from the human health point of view is the part of estrogens (estradiol, estradiol-alpha or estrone) which will be metabolized in[to] catechol derivatives in target tissues." However, as noted in the US discussion in Question 13 above, the EC has not provided any evidence to indicate that either estradiol 17α or estrone can be converted to catechol estrogens in humans. The EC comments that this concern "is the reason for which it is necessary to perform a complete residue analysis with more powerful detection methods." However, upon review of the exhibits put forward by the EC, it appears as though the EC has already done just this. In Exhibit EC-51A, it is concluded that "[a]n almost complete reassessment of estrogen residues in edible tissues of estradiol-17β treated animals has been performed."[76]

55. The EC also notes that "the fact that exposure to catechol metabolites does not cause mammary tumorigenesis does not necessarily negate the possibility that the catechol metabolites formed in mammary tissue play a role in mammary tumorigenesis ... because administered

[74] *See* Appellate Body Report, para. 186.
[75] *See generally* US Comments on the Experts' Responses, para. 44.
[76] The results of this comprehensive study were not discussed by Dr. De Brabander, the Panel's expert in residue chemistry.

metabolites may not reach levels in mammary tissue comparable to those achieved by metabolism of estradiol to the catechols within the mammary itself." However, the credibility of this statement relies on the comparison between concentrations of catechol estrogens in the mammary tissue of experimental animals with those actually found in normal human mammary tissue in vivo. To date, results of this critical comparison have not be reported by the EC.

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

57. Question 18: The EC notes its agreement with the statement of Dr. Cogliano, but apparently only refers to a limited portion of Dr. Cogliano's response. Dr. Cogliano concludes that "the issue, though is whether [] genotoxicity would occur at levels found in meat residues." As to this issue, "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans." Therefore, Dr. Cogliano's response appears to directly contradict the EC's assertion that levels of hormone residues found in meat from treated cattle would be genotoxic.

58. As noted by the United States in its Comments on the Experts' Responses, while Dr. Guttenplan notes that there is evidence that estradiol 17β is genotoxic, he does not conclude that it would be genotoxic at levels found in residues in meat from cattle treated for growth promotion purposes. Indeed, his statement that while "an adverse effect cannot be ruled out, [] it is unlikely if good veterinary practices are followed,"[78] appears to indicate that he is not of this opinion.[79]

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

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

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

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

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

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

demonstrate a risk from meat from cattle treated with estradiol 17β for growth promotion purposes, including that estradiol 17β is genotoxic at levels found in residues in meat from treated cattle.

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

61. Question 19: The EC notes that it agrees with the "thrust" of Dr. Guttenplan's response, and then appears to pose a question and offer a response which is not in fact included in Dr. Guttenplan's response. The United States analyzes Dr. Guttenplan's response in detail in paragraph 38 of its Comments on the Experts' Responses. The EC also notes that "although DNA repair can occur, it presumably is occurring at all doses and the fraction of DNA damage repaired probably does not change at physiological levels, because the repair enzymes are unlikely to be saturated." This statement, which the EC attributes to Dr. Guttenplan, appears to further highlight the fact that the EC should have (but failed to) taken DNA repair mechanisms into account in its Opinions. Further, since, as confirmed by the EC, the repair enzymes are not saturated under physiological conditions, then it stands to reason that these enzymes have the capacity for increased activity when exposed to xenobiotics or elevated concentrations of endogenous genotoxic substances.[82] Therefore, increased activity of DNA repair enzymes is a protective mechanism against DNA damage. Of course, the capacity for increased enzyme activity is finite and can be overwhelmed (*i.e.*, saturated) in the face of very high exposure to genotoxic compounds, but there is no evidence that this will occur in response to the very low amounts of estradiol 17β in meat from treated cattle.

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

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

64. The EC also notes that Dr. Boisseau's statement "cannot be accepted scientifically" because "[i]n the EC's view, it is beyond doubt that there is a link between 17β-oestradiol exposure during development ... and the risk of breast cancer later in life." However, the "EC's view" of the scientific

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

evidence and what the scientific evidence actually demonstrates are two distinct concepts. The EC has failed to demonstrate that the scientific evidence actually supports its view.[83]

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

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

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

68. The EC also notes that, since the original *Hormones* dispute, the EC "has been consistently arguing [that] the genotoxicity of oestradiol-17β is no longer seriously disputed and has now for the first time been accepted and written in the 1999 JECFA report." On the one hand, the fact that the EC has been arguing a point does not mean that the point is actually supported by scientific evidence. In fact the EC made this argument in the original dispute and is here simply trying to overturn established WTO findings. Indeed, the experts have confirmed that, insofar as the issue of genotoxicity relates to hormone residues in meat from cattle treated for growth promotion purposes, the evidence does not demonstrate a genotoxic effect.[85] On the other hand, the experts have confirmed that JECFA's statement of "genotoxic potential" did not affect its ultimate conclusion that the use of the hormones as growth promoters in cattle is safe.[86]

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[83] *See* the Responses of Drs. Boisseau, Boobis, Cogliano and Guttenplan to Panel Question 26 ("Does the scientific evidence referred to by the European Communities, in particular any epidemiological studies, identify a relationship between cancer and residues of hormonal growth promoters? In its risk assessment of 1999, the European Communities makes reference to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities. Can a link be established between these statistics and the consumption of meat from animals treated with the hormones at issue?") The experts unanimously confirm that the EC has not demonstrated a link between consumption of hormones residues in meat and breast cancer.

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

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

[86] *See* US Comments on the Experts' Responses, para. 41.

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

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

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

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

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

> [t]estosterone and progesterone are negative in genotoxic assays. Zeranol can induce transformation of breast epithelial cells in culture with efficiency similar to that of estradiol, but the mechanism is not known, and it is negative or marginally active in

[87] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.
[88] *See* Panel Report, *Japan – Apples (21.5)*, paras. 8.145-8.146.
[89] *See* US Comments on the Experts' Responses, para. 41 and fn. 97 for discussion of the responses of Drs. Cogliano and Guttenplan. *See also* US Rebuttal Submission, paras. 38-40.

> other assays. Trenbolone is either negative or marginally active in in vitro genotoxic assays. MGA is negative in genotoxicity assays. Any genotoxic effects of the five hormones are likely to be minimized by good veterinary practice. My reply for the hormones would not have been different in September 2003 (SCVPH 2002 Opinion).

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

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

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

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

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

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

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

78. Question 24: The EC avers that the experts' responses on confounding factors "also undermine indirectly the position of the US" without providing any argument or explanation for why this is so. The EC cites again to a study regarding the frequency of breast cancer (cited in its 1999 Opinion) and purports to draw a link between the use of hormones for growth promotion purposes and the incidence of cancer. The experts have dismissed this link in their responses to Panel Question 26 (Boisseau: (citing to his response to Question 23) "the hormones in dispute have already been used as growth promoters over a sufficient number of years, the epidemiological studies in humans already carried out in this domain have failed to identify any relation between the occurrence of hormonally dependent tumours and the consumption of meat containing hormonally active residues resulting from the treatment of cattle with growth promoters; Boobis: "[t]here is no scientific evidence demonstrating any association between consumption of meat from animals treated with growth promoting hormones and the risk of cancer in humans; Cogliano: "[t]he data [relating to the difference in breast cancer rates] are not sufficiently specific to establish a link between these observations"; Guttenplan: "[t]he epidemiological studies do not identify a relationship between cancer and residues of hormonal growth promoters. The references to the higher rates of breast and prostate cancer observed in the United States as compared to the European Communities are not very convincing as there is considerable variation in rates in different geographical locations. Also, the differences in rates of breast and prostate cancer observed in the United States as compared to the European Communities are relatively small.")

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

80. The EC argues that Dr. Boobis has taken an "absolutist" approach, and attacks his response by alleging that Dr. Boobis requires "positive proof of harm," and that rather evidence should be provided of a lack of possible harm. The Appellate Body noted the following regarding the alleged need to provide evidence of a lack of harm: " [i]n one part of its Reports, the Panel opposes a requirement of an 'identifiable risk' to the uncertainty that theoretically always remains since science can never provide absolute certainty that a given substance will not ever have adverse health effects. We agree with the Panel that this theoretical uncertainty is not the kind of risk which, under Article 5.1, is to be assessed."[93] As is clear from its comments on Dr. Boobis' response, rather than providing actual scientific evidence of a risk to consumers from the consumption of residues in meat from cattle treated for growth promotion purposes and basing a measure on the risk assessment drawn from that evidence, the EC would instead opt to focus on the very theoretical uncertainties described by the Appellate Body in support of its ban on meat and meat products from cattle treated with estradiol 17β. All of this is a distraction from Dr. Boobis' response, which categorically notes that the three recent studies referred to by the EC "do[] not confirm a risk to human health from the consumption of meat from cattle treated with growth promoting hormones."

81. The EC agrees with the comments of Dr. Cogliano, which is surprising since Dr. Cogliano's comment on the Norat study is that it indicates a risk to human health from meat generally[94], and his comment on the other two studies is qualified by the fact that "the exposure levels found in these studies are higher than those found in meat residues." The EC cites very selectively to

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

[93] Appellate Body Report, para. 186.

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

Dr. Guttenplan's response, which is understandable since he concludes the following regarding the first EC study (Liu and Lin): "the results were obtained in cultured cells and the relevance to human exposure to hormone-treated [meat] cannot be extrapolated from this study because of a myriad of uncertainties in such extrapolation." He concludes the following regarding the second and third studies: "[t]he other two studies do not confirm a risk from hormone-treated meat." The results of the Liu and Lin paper are questionable due to lack of a dose response. The authors claim to have data that meat and serum from zeranol-implanted cattle are mitogenic and estrogenic, but their reports are all in abstract form (not publicly available). The US FDA has approached the authors for more information, but they have not responded to repeated requests.

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

83. The EC notes that it "advanced this [epidemiological] argument to demonstrate that the scientific uncertainty is growing concerning the harmless nature of the residues of these hormones." (Emphasis in original). However, as evidenced by the experts' responses, the EC has demonstrated no such uncertainty. Further, as noted by the Appellate Body, "theoretical uncertainty is not the kind of risk which, under Article 5.1, is to be assessed,"[95] and "the existence of unknown and uncertain elements does not justify a departure from the requirements of Articles 5.1, 5.2 and 5.3, read together with paragraph 4 of Annex A, for a risk assessment."[96]

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

[95] Appellate Body Report, para. 186.

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

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

86. Question 27: It is unclear why the EC thinks that the results of Stephany are "completely different" than those used to support approval of estradiol 17β as reported in the 1999 JECFA Report. The concentration of estradiol 17β reported by Stephany in "M/LQ domestic US beef", 0.03 ppb (equal to 30 nanograms/kilogram), is well within the range of estradiol 17β concentrations in muscle reported by JECFA which range from 0.5 - 117 nanograms/kilogram. Although the average concentrations are correctly quoted from Table 5 of Stephany's paper, Stephany uses the median values to make the statement that "it is estimated that the median dietary intake of 17β-estradiol via a 250 gram steak of 'Hormone Free Cattle' is less than 2.5 nanogram and via 250 gram 'beef' of 'Hormone Treated Cattle' is 5 nanogram", *i.e.*, a 2-fold difference. It is assumed that Stephany used the median values for this comparison because these values, not average values, are most appropriate to use when assessing lifetime dietary exposure to a residue or contaminant in food (*see* 1999 JECFA report, p. 83). Thus, the 7.5-fold difference in estradiol-17β concentrations in beef between treated and untreated cattle cited by the EC may be considered an exaggeration.

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

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

89. The EC notes that Dr. De Brabander's statement is "very informative", but the United States notes that Dr. De Brabander's response fails to cite any scientific evidence in support of its

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

[98] Exhibit EC-78.

[99] Exhibit EC-51C.

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

conclusions, which appear to miss the point of the Panel's query. The Panel's question speaks to differences in the fundamental composition of the hormones in their basic form (*i.e.*, is estradiol 17β in the human body the same as estradiol 17β residues in meat). Dr. De Brabander's response provides speculation as to how the body breaks down or metabolizes the hormone, making a vague reference to body builders. The process of metabolization of the hormones has been discussed in detail above.[101] Further, the EC's endorsement of Dr. De Brabander's "finding that the residues of the endogenously produced natural hormones in cattle are in the 17α form (inactive) while the use of the natural hormones for growth promotion purposes may lead to residues in the β form (active form)," suggests that tissue residues of estradiol 17β in cattle treated with estradiol 17β for growth promotion purposes are qualitatively different from residues in untreated cattle. This is incorrect, as demonstrated by the results of the EC's own "17 Studies",[102] which showed that edible tissues from untreated cattle and cattle treated with a growth-promoting implant contain both estradiol 17β (muscle, liver, kidney) and estradiol 17α (liver and kidney only (no muscle)).

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

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

92. The United States notes that the residue data used to support approval of the growth promoting hormones are reviewed in the 52nd JECFA Report. Included in this Report is a very detailed description of the method (developed in 1979 and revised in 1982 and 1983) used to generate these residue data and four pages of data which describe the method's performance (percent recovery, range of assay detection, intra- and inter-assay variability, assay precision). Therefore, all of the information required to evaluate the methods used to generate the residue data used by JECFA in its determinations have been publicly available since 1999. Despite this fact, neither the EC nor the scientific expert on residues (Dr. De Brabander) has provided a scientific review or analysis of these data explaining why or how the methods are "no longer reliable today", nor do they provide any reasons for why the methods were not adequate to derive MRLs. Instead, they opt to dismiss them as unreliable simply because they are "old." As explained in the US Comments on the Experts' Responses at footnote 193, JECFA has specific and extensive requirements for residue data. Therefore, these "old" data were critically reviewed by JECFA experts in 1999 and deemed to be of sufficient quality to assess the human food safety of hormone residues in beef.

93. Question 30: The EC attempts to dismiss the response of Dr. Boisseau for the same unfounded reason cited in its comments on Question 29 above. The EC opines that Dr. Boobis is

[101] *See*, *e.g.*, Questions 13 and 17 above.
[102] Exhibit EC-78.
[103] Responses to Questions from the Panel of Dr. Hubert De Brabander ("Dr. De Brabander Responses") (Question 29), p. 3.

"clearly wrong" because, according to the EC, it has completed a "detailed exposure assessment" for the three natural hormones. Yet, both Drs. Boobis and Boisseau, upon review of the EC's materials, disagree. Dr. Boobis notes, as has been argued by the United States, that rather than evaluating actual residue levels of the natural hormones, the EC instead concocts several misuse scenarios in its attempt to demonstrate a risk to consumers.[104]

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

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

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

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

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

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

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

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

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

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

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

100. The EC quotes Dr. Boobis' comment that, over time "it became clear that exposure to the natural hormones, albeit at levels appreciabl[y] higher [than] that found in meat from treated cattle, could have adverse effects on human health," as support for its arguments. However, Dr. Boobis' conclusion, which notes that recent epidemiological evidence demonstrated that hormones caused effects "at levels appreciably higher than that found in meat from treated cattle" contradicts the EC's argument that the exponentially lower levels of hormone residues in meat from treated cattle pose a risk, and instead supports arguments put forward by the United States in its submissions to the Panel.[109]

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

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

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

104. Question 35: The EC comments that Dr. Boisseau agrees that the data evaluated by JECFA on MGA "date[s] from the 1960s and 1970s". The EC refers to its comments on Question 34 to

[109] *See*, *e.g.*, US Rebuttal Submission, paras. 38-39.
[110] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

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

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

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

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

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

109. The EC also cites Dr. Boobis' statement that "once a compound is identified as an in vivo DNA-reactive mutagen, or as causing a carcinogenic response via a genotoxic mode of action, no exposure is considered without risk." As has been made clear in Questions 19 and 20 above,

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

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

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

[114] *See* Question 14 above.

Dr. Boobis has concluded that the evidence on the hormones, including estradiol 17β, does not indicate that they are in vivo DNA-reactive mutagens (Dr. Boobis concludes: "[t]here is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this. Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance.").

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

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

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

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

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

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

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

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

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

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

118. Finally, the EC fails to note Dr. Boobis' ultimate conclusion which is that, even assuming the lower levels of circulating estradiol 17β proposed by Paris *et al*., the simple fact is that "exposure is via the oral route, and bioavailability by this route is very low (<5%) (Fortherby, 1996). In addition, very little of the absorbed hormone will be free, over 95% being bound to plasma proteins such as SHBG. Such binding reduces the biological activity of the hormone (Teeguarden and Barton, 2004). Hence, the JECFA ADI would appear to be appropriate for all groups of the population."

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

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

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

119. Question 41: The EC comments that the replies of Drs. Boisseau and Boobis are "not entirely convincing," and in support of this claim cites to alleged risks concerning "estradiol-17-esters and estradiol-alpha found in residues in treated steers." As noted by the United States in Questions 13, 17 and 28 above, the EC's suggestion that estradiol 17α is present in beef and may be further metabolized in the human consumer to catechol estrogens is weak for several reasons: (1) Maume *et al.*[120] demonstrated that estradiol 17α concentrations are elevated only in liver and kidney, but not muscle, following administration of a single implant (muscle is the tissue most often consumed); (2) the EC attempted but was unable to provide evidence estradiol 17α can be converted to catechol estrogens by human intestinal cells[121]; and (3) estradiol 17α does not appear to be carcinogenic[122] and thus does not fit into the EC's theory that estrogens are genotoxic carcinogens (via catechol metabolites).

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

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

122. The EC comments that the responses of Drs. Boisseau and Boobis "are based again on the assumptions that this hormone [estradiol 17β] is not genotoxic and that the rate of endogenous production by prepubertal children is correctly cited in the JECFA report." These are not "assumptions", however, but reflect the views of both experts on the state of the scientific evidence relating to estradiol 17β. Indeed, both Dr. Boobis and Boisseau have concluded, based on a review of the EC's Opinions, the science cited therein, and a review of relevant recent scientific literature that estradiol 17β is not genotoxic in vivo, nor would it be genotoxic at levels found in residues in meat from cattle treated for growth promotion purposes.[125]

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[120] Exhibit EC-78.

[121] Exhibit EC-51C.

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

[123] *See* US Comments on the Experts' Responses, paras. 27-30.

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

[125] *See*, *e.g.*, Dr. Boobis Responses (Question 16), p. 20 ("[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine activity"; [t]he evidence is against any direct interaction of oestradiol or its metabolites with DNA."); Dr. Boobis Responses (Question 18), p. 22 ("[t]o reiterate, whilst there are reliable studies demonstrating the genotoxicity of oestradiol in certain in vitro tests, the evidence is against any genotoxicity in vivo.") (note that the EC's own guidelines on genotoxicity testing "require confirmation of an in vitro positive using an appropriate in vivo assay." *See* CVMP (2004). Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing, European Medicines Agency, London); Dr. Boobis Responses (Question 19), p. 22 ("[t]here is no good evidence that oestradiol is genotoxic in vivo or that it causes cancer by a genotoxic mechanism. Indeed, the evidence is against this.

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

124. Question 43: The EC disagrees with Dr. Boisseau, who opines the estradiol 17β is "inactive orally" because, according to the EC "[t]his is simply factually wrong! Oestradiol 17β is routinely administered to humans as a powder or in the form of pills that are taken orally." In support of its argument, the EC cites to Lampit *et al*. However, the Lampit study very clearly indicates that, to overcome the low bioavailability of estradiol 17β, very large amounts of the hormone must be administered orally to achieve a therapeutic effect. The EC comments that there are "no doubts that oestradiol-17β is orally active." As noted in Question 8 above, while it is true that estradiol 17β is administered orally for some indications, because its bioavailability is so low, very high doses are required to elicit the desired therapeutic effect. For example, therapeutic doses of estradiol 17β for oral administration range from 0.5 - 4.0 milligrams,[126] or 10,000 - 40,000 times higher than the 30-50 ng/person/day derived from eating beef from cattle treated with estradiol 17β for growth promotion purposes. In addition to high doses, orally administered estradiol 17β are manufactured as micronized formulations (particle size < 10 microns) to further increase bioavailability. Even after micronization, the bioavailability of a 2 mg dose of estradiol 17β is still only about 5%.[127]

125. The EC also notes that it has provided "credible recent evidence" that "the bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is taken into account." However, as noted in Question 41 above, review of the section of the EC's Second Written Submission which discusses bioavailability of hormone residues (paragraphs 123 to 124) reveals no information to support the statement that bioavailability of these residues is greater than or equal to 10%. In fact, as the United States has pointed out in its Comments on the Experts' Responses,[128] the EC has failed to provide any evidence to contradict the statement by Dr. Boobis indicating that the bioavailability of natural hormone residues < 5-10%. This statement is supported by several peer-reviewed publications.[129]

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

127. The EC asserts that "[n]either Dr. Boisseau nor Dr. Boobis provide a specific reply to [Dr. Guttenplan's reply concerning prepubertal children]," a statement that the United States finds perplexing based on a review of Dr. Boobis' very detailed reply to the question of whether estradiol

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Hence, the scientific evidence does not support the EC on this issue, that the levels of the hormones in meat from treated cattle are not of relevance.") (Emphasis added); Dr. Boisseau Responses (Question 13), p. 11 ("[i]n conclusion, the EC risk assessment did not support that residues of oestradiol-17β, despite the genotoxic potential of this hormone, can initiate and promote tumours in humans.") *See also* Dr. Cogliano Responses (Question 18), p. 1 ("it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans.")

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

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

[128] *See* US Comments on the Experts' Responses, paras. 27-30.

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

17β in beef presents a risk factor for prepubertal children.[130] Indeed, Dr. Boobis takes into account the possibility that circulating levels of estradiol 17β are lower than previously estimated. Using this assumption, together with the well-supported conclusion that bioavailability of estradiol 17β is very low (< 5%), Dr. Boobis shows very convincingly that consumption of beef from cattle treated with estradiol 17β for growth promotion does not approach the ADI and thus does not pose a risk to prepubertal children.

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

129. Question 44: The EC cites Dr. Boisseau's opinion that "Codex did not adopt any guideline for GVP aimed at minimizing the occurrence of veterinary drug residues in animal derived food" as supporting its argument.[131] However, the EC does not clarify to what argument it is referring. The United States notes that Dr. Boisseau's statement that Codex has not adopted a guideline on GVP is unexceptional, and reiterates that the essential analysis is whether the EC, in its purported risk assessment, has properly examined and evaluated a risk from the failure of good veterinary practices (per Articles 5.1 and 5.2 of the SPS Agreement). The EC appears to accept that it must evaluate this risk, if the assumption of failure of controls is to be a mainstay of its purported assessment, by citing to guidance from the Appellate Body.

130. As the United States has demonstrated, the EC has failed to assess a risk from failure of controls.[132] The experts have confirmed this fact.[133] The EC notes that "there is an important difference between the theoretical assumption of respecting [good veterinary practices] and real life," but has simply not evaluated the risk of failure of good veterinary practices, nor has it even demonstrated through scientific evidence that, save for the most unrealistic misuse scenarios (extreme overdosing), residues of the hormones would reach violative levels.[134]

131. Question 45: The EC cites Dr. Boisseau for the proposition that Codex recommendations "are only meaningful in countries where GVP are effectively implemented." This is so because, as noted by the United States in its Comments on the Experts' Responses at footnote 222, approvals of or standards relating to veterinary drugs (or any substance for that matter) are not premised on the notion of misuse. Any drug can be misused, and most drugs can be harmful if consumed at extremely high, unrealistic levels. If misuse were used as a baseline for veterinary drug approvals, no drugs would ever be approved. However, as noted by the Appellate Body, for purposes of an SPS measure, a

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

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

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

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

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

Member may take misuse or failure of controls into account as part of their basis for that measure, but they must actually evaluate or assess that risk. The United States has demonstrated at several points in its Rebuttal Submission and Comments on the Experts' Responses that the EC has failed to evaluate this risk.[135] The experts have confirmed this fact.[136] The experts have further confirmed that the scientific evidence relied on by the EC for its conclusion that artificial misuse scenarios will lead to violative levels of hormone residues does not support that conclusion.[137]

132. As noted by the United States in its Comments on the Experts' Responses at paragraph 101, the issue of conditions of use, and whether the EC has evaluated the risk from misuse, is essential to a determination of whether it has based its permanent ban on estradiol 17β on a risk assessment within the meaning of Articles 5.1 and 5.2 of the SPS Agreement and whether its provisional ban on the five other hormones is based on available pertinent information within the meaning of Article 5.7 of the SPS Agreement. The fact that the EC has raised the issue of misuse[138] and devoted considerable resources to demonstrating the potential consequences of misuse implies that it already recognizes that there are conditions under which residues of the six hormones used for growth promotion are safe. In other words, if, as argued by the EC, the six hormones pose a risk at levels found in residues in meat from cattle treated according to good veterinary practices, then why has the EC tried to refocus attention on the specter of misuse? The only germane question then would be whether there are particular conditions of use under which there would be a health risk.

133. Question 47: The EC comments that Dr. Boisseau's response is "partially false", because he has concluded that "the [EC] did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the [EC] took into account relevant control mechanisms with respect to GVPs in place in the USA." The simple fact is that the experts have reviewed the EC's Opinions and the studies cited therein, and have determined that the EC has failed to assess this risk.[139] Insofar as Dr. De Brabander has spoken to the issue of whether or not the EC's Opinions adequately evaluate the risk from misuse, the United States addresses his comments in its Comments on the Experts' Responses at Section C.6.

134. The EC claims that the "evidence available does show that such misuse or abuse occurs frequently, because these hormones are administered in combinations and the farmers have incentives to apply multiple doses." Each of these conclusions is speculative and unsupported by the evidence presented. The experts' responses have confirmed this fact (note that none of the experts cites to any of this purported evidence of "frequent" misuse), and the United States has demonstrated at great length in its Rebuttal Submission at paragraphs 54-66 and Comments on the Experts' Responses at paragraphs 105-106 that there is in fact great disincentive for commercial feedlot operators to misuse growth promoters. Programs administered by the US Government include setting safe levels for veterinary drugs; monitoring for violative residues; and inspection of meat at the ante-mortem, post-mortem and processing stages. As large commercial operations, US feedlots have great incentive to comply with the regulations set and enforced by USDA and the FDA. In support of its claim that "farmers have incentives to apply multiple doses" the EC has cited in previous submissions to a document entitled "Beef Cattle Implant Update" authored by Dr. Dee Griffin (Exhibit US-27). The United States has submitted a letter from Dr. Griffin in which he explains that this document does not

[135] *See* US Rebuttal Submission, Section II.B.4; US Comments on the Experts' Responses, Section C.6.
[136] *See* Dr. Boobis Responses (Question 48), p. 42; Dr. Boisseau Responses (Question 48), p. 24.
[137] *See generally* Dr. Boobis Responses (Question 62), pp. 50-52; *see* US Comments on the Experts' Responses, Section C.6; US Rebuttal Submission, Section II.B.4.
[138] *See*, *e.g.*, Replies to Questions from the Panel after the First Substantive Meeting by European Communities, para. 91.
[139] *See* Questions 44-46 above.

support the conclusions taken from it by the EC, and confirms that there is absolutely no incentive (either economic or legal) to misuse growth promoting implants.[140]

135. Question 48: The EC argues that the responses of Drs. Boisseau and Boobis are misguided because "as the [EC] has explained several times in previous questions, [a quantitative assessment] is not required under the SPS Agreement as interpreted by the Appellate Body." The United States has addressed both: (1) the notion that experts should be taking legal considerations into account, and (2) the EC's overly simplistic reading of the Appellate Body statement above.[141] In any event, the EC does not rely on its assertion that it may just produce a qualitative assessment, but instead states that "the [EC] has nevertheless performed a quantitative dose-response assessment in particular with regard to prepubertal children." Thus, it is patently unclear how on the one hand the EC can dismiss the comments of the two experts for analyzing the EC assessment as though it should have been a quantitative assessment while on the other claiming that it has conducted just such a quantitative assessment.

136. The experts do not agree with the EC that it has conducted a quantitative assessment. Dr. Boobis: "There was no attempt to evaluate the risks from the resultant exposures on misuse or abuse, either in the papers cited or by the SCVPH (2002) in their evaluation of these studies. Indeed, the SCVPH (2002) simply noted that 'Therefore, these data have to be considered in any quantitative exposure assessment exercise', without undertaking such an exercise." Dr. Boisseau: "the European Communities did not conduct any quantitative risk assessment for growth promoters, it is not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses." As described in detail in the US Comments on the Experts' Responses, Dr. De Brabander does not appear to offer an opinion as to whether the EC has indeed assessed risks to human health from misplaced implants or improper administration.[142]

137. The EC also claims that "it is obvious that the higher levels of residues that will inevitably result from misuse or abuse of these hormones will also exceed the ADIs and MRLs recommended by JECFA." However, as demonstrated by the United States in its Rebuttal Submission[143] and confirmed by Dr. Boobis (the only expert to specifically analyze the misuse studies conducted by the EC), this conclusion is unsupported by the scientific evidence. Dr. Boobis (Question 62): "the data generated by the EU research in question [*i.e.*, concerning artificial misuse scenarios] do not provide any indication that it is not possible to conduct a risk assessment of the hormones used as growth promoters. Nor do they provide any indication that even such misuse or abuse as investigated gives rise to undue risk from the resultant residues, as intake would only very rarely exceed the ADI and then only on a rare occasion."

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

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[140] *See* Letter from Dr. Dee Griffin explaining results of Beef Cattle Implant Update. (Exhibit US-28).
[141] *See*, *e.g.*, Section B.2.
[142] *See* US Comments on the Experts' Responses, Section C.6.
[143] *See* US Rebuttal Submission, Section II.B.4; US Comments on the Experts' Responses, Section C.6.

139. Finally, the EC comments that Dr. Boobis' reference to "probability" of a risk is inappropriate in light of the Appellate Body's interpretation that a Member must identify the "possibility" of a risk. The United States addresses the EC's interpretation of the Appellate Body's decision at several points above.[144] However, the distinction between "probable" and "possible" is irrelevant to an analysis of what the EC has or has not accomplished in its "risk assessment" in light of the fact that it has asserted that "the [EC] has [] performed a quantitative dose-response assessment," which would by its very nature account for probability. The experts do not believe that the EC has completed such an assessment.

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

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

142. The United States also notes with interest the EC's agreement with the comments of Dr. De Brabander, who is of the opinion that "there are no other measures possible to the [EC], other than a complete ban, which could address risks arising from misuse and failure to follow good veterinary practices." Dr. De Brabander's response appears to indicate that there is no way to control the use of these substances other than a ban. If this is so, and a complete ban is the only possible remedial measure, then the controls currently employed by the EC for the administration of the hormones to cattle are also inadequate. Further, as demonstrated by the United States, a ban is not, as it appears to have been cast by Dr. De Brabander and the EC, a iron clad assurance that no misuse will ever occur. This conclusion is supported by evidence of an active, illegal black market for the use of hormones in the EC, which chose to impose a ban on their use.[145]

143. Question 51: The EC fails to mention that Dr. Boisseau notes that "the European Communities did not conduct any quantitative risk assessment for growth promoters, [and] it is [therefore] not possible to say that the scientific evidence referred to by the European Communities assesses the risk to human health from residues resulting from these misuses/abuses." The United States also notes that Dr. Boobis has provided a detailed analysis of the studies relied on by the EC as evidence of misuse leading to residue levels higher than Codex MRLs or ADIs – he concludes that the EC materials do not threaten these levels even under extreme circumstances.[146] The EC states that it "agrees" with Dr. De Brabander's opinion. The United States addresses the notion that JECFA's data is "older" and therefore inadequate at paragraphs 22, 92, and 102-104 above, and paragraphs 92 and 111 of its Comments on the Experts' Responses. The United States addresses the inapplicability of the other conditions raised by Dr. De Brabander to the situation at hand (*i.e.*, ban on imported meat) at Section C.6 of its Comment on the Expert Responses.

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

[145] *See* US Rebuttal Submission, Section II.B.4.

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

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

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

146. The EC attempts to dismiss Dr. Boobis' response due to the fact that he concludes that "all of the major reviews in this topic (*i.e.*, genotoxicity) have concluded that whilst there are data gaps, there is no evidence that low level exposure is causing harmful effects in humans," and "[t]he carcinogenic effects observed are entirely consistent with a hormonal mode of action that exhibits a threshold that would be well above the intake arising from consumption of meat from treated cattle." The EC focuses on the reference to data gaps as in some fashion supporting its decision to permanently ban the import of meat from cattle treated with estradiol 17β for growth promotion purposes. The EC fails to emphasize: (1) Dr. Boobis' conclusion that "there is no evidence that low level exposure is causing harmful effects in humans; (2) Dr. Boobis' response to the Panel's question concerning any potential data gaps (Question 62) (data presented by the EC "do not demonstrate any important gaps, insufficiencies and contradictions in the scientific information used by JECFA"); (3) Dr. Boobis conclusions to other Panel questions relating to genotoxicity (*e.g.*, Question 18 ["the evidence is against any genotoxicity in vivo."]); (4) relevant discussion from the Appellate Body ("science can never provide absolute certainty that a given substance will not ever have adverse health effects. We agree with the Panel that this theoretical uncertainty is not the kind of risk which, under Article 5.1, is to be assessed.")[147]; and (5) relevant discussion from the compliance panel in *Japan – Apples (21.5)* (scientific conclusions reached in a risk assessment must actually be supported by the scientific materials cited therein).[148]

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

148. Question 53: The EC notes, regarding Dr. Guttenplan's response, that "this is still another kind of uncertainty that should be taken into account by the Panel in deciding whether the evaluations by JECFA are credible and reliable." The United States reiterates that the EC has adopted a permanent ban on estradiol 17β based on what it claims is a risk assessment, as appropriate to the circumstances, within the meaning of Article 5.1 of the SPS Agreement. Theoretical uncertainty may

[147] Appellate Body Report, para. 186. Recall that the EC claims to have imposed its permanent ban on estradiol 17β based on a risk assessment within the meaning of Article 5.1.

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

not serve as the basis for such an assessment.[149] Further, the EC fails to note Dr. Guttenplan's conclusion that "because the concentrations of all of the hormones in beef are so low, [] they would be unlikely to affect the potency of estrogen." Finally, Dr. Guttenplan notes that "no experiments on effects of combinations were performed, so some uncertainty exists there." If the scientific evidence does not, through a lack of study, demonstrate a risk or support the conclusion that combinations with estradiol 17β would increase risks, the EC may not rely on this conclusion in its "risk assessment" within the meaning of Article 5.1 of the SPS Agreement.[150]

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

150. Question 54: As noted in Question 16 above, the EC claims that Codex has set a "qualitative" appropriate level of protection, whereas the EC has set a "quantitative" level of protection. Yet the EC then argues that it achieves this "quantitative" level of protection with a "qualitative" risk assessment. The logic of the EC's argument does not follow. Further, the EC appears to have recast its level of protection as one of "no risk" as opposed to "no additional risk." A "no risk" level of protection (assuming that the EC were actually able to demonstrate a risk to human health from residues of the hormones in its Opinions) would presumably capture, and require the cessation of, several existing uses of the hormones in cattle in the EC as well as the consumption of numerous foods containing any of the six hormones.

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

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

153. Question 55: The EC requests that the Panel "disregard [the comments of Drs. Boisseau and Boobis] because they are purely theoretical and for the additional reason that they come from two experts who have never done any specific research on these hormones nor have they ever published something on these substances." The United States has addressed similar objections by the EC in its comments above. In this instance, the United States would also note that the Panel's question is one of interpreting or analyzing materials and conclusions drawn in a "risk assessment." Both experts are

[149] *See* Appellate Body Report, para. 186.
[150] *See* Panel Report, *Japan – Apples (21.5)*, paras. 8.145-8.146.
[151] EC Comments on the Experts' Responses (Question 39).

eminently qualified in conducting, interpreting and analyzing risk assessments and Dr. Boobis has published on matters of risk assessment theory.[152] The EC's assertion that these experts are not qualified to respond to the Panel's questions is spurious, and is a weak attempt to distract from the responses of Drs. Boobis and Boisseau, *i.e.*, that the EC has not evaluated the "additive risks" in its Opinions or scientific materials.[153]

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

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

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

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

158. The EC also notes that "the additive risk needs to be carefully evaluated. For instance, trenbolone as such has a complex hormonal activity (at the same time progestin, androgen and glucocorticoid)." This comment appears to presuppose that JECFA did not engage in such a careful evaluation. The experts have confirmed, to the contrary, that JECFA did in fact evaluate these additive risks. Further, the EC has not provided scientific evidence to support the claim that

[152] *See Curriculum Vitae* of Drs. Boobis and Boisseau.
[153] The comments of Drs. Boisseau and Boobis are quoted in Question 54 above.

trenbolone mimics the biological effects of glucocorticoid. In fact, there is evidence in the literature that trenbolone exerts antiglucocorticoid activity (Meyer H. Biochemistry and physiology of anabolic hormones used for improvement of meat production. APMIS 2001; 109:1-8). With respect to progestin, one of the EC's "17 Studies"[154] provided evidence that 17β-TBOH, the primary metabolite of trenbolone found in bovine muscle tissue, binds to the bovine progestin receptor. However, binding of trenbolone and its metabolites to the human progestin receptor was not investigated, and it must be emphasized that hormone binding in vitro is not equivalent to demonstrating that the hormone actually exerts receptor-mediated effects in vivo.

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

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

> The European Communities thinks that, given the conditions of theses uses of oestradiol-17β (limited number of treated animals, limited use in the life of these animals and very low probability to see these animals slaughtered after treatment), the exposure of consumers to oestradiol-17β residues resulting from these uses can be considered as negligible. If this EC assumption can be accepted, it raises nevertheless a problem of principle as it represents an exception regarding the very strict position of EC stating that it is not possible to accept any increase of the exposure of consumers to oestradiol-17β residues. As soon as the European Communities accepts to considers these residues resulting from these therapeutic and zootechnical use of oestradiol-17β as negligible, it enters in a quantitative, or at least in a semi quantitative, exposure assessment procedure for these oestradiol-17β residues and, starting from that, it has no good reason to object to consider a wider exposure assessment covering all the residues resulting from the different sources of oestradiol-17β.

161. The EC agrees with the conclusion of Dr. Guttenplan. The United States notes that Dr. Guttenplan's opinion, that zootechnical or therapeutic use would "not constitute a hazard for public health" appears to indicate that he is of the opinion that low levels of the hormones are not genotoxic. This comports with his opinion that an adverse effect is " unlikely if good veterinary practices are followed."[155]

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[154] Exhibit EC-15.
[155] Dr. Guttenplan Responses (Question 15), p. 4.

162. Question 58: The EC's comments fail to address the responses of the experts. Dr. Guttenplan: "[t]his is indeed a very weak statement by the EC." Dr. Boobis: "[w]ithin quite broad limits, higher exposure would not result in any increase in risk." Dr. Boisseau: "[t]he European Communities did not assess quantitatively the extent to which residues of growth promoting hormones in meat contribute to 'additive risks arising from the cumulative exposures of humans to multiple hazards, in addition to the endogenous production of some of these hormones by animals and human beings'." The EC cites again to the 2002 Report on Carcinogens, which has been discussed in detail by the United States in its comments on the EC's comments on Question 12 above and in its Rebuttal Submission.[156] As demonstrated in the US comments above, the EC has not in fact "shown that the level of residue formation in meat can be significantly higher and may contain residues from different metabolites."

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

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

165. Second, the notion that the United States or JECFA must assure the EC that there is no risk of adverse effects from the use of the five hormones is simply a flawed attempt to distract from the issue at hand. As noted by the Appellate Body, "science can never provide absolute certainty that a given substance will not ever have adverse health effects."[157] In other words, it is impossible to prove the absolute negative, despite the EC's demand for such proof from the United States and several of the

[156] *See* US Rebuttal Submission, paras. 38-40.
[157] Appellate Body Report, para. 186, citing Panel Report at paras. 8.152-8.153.

experts. This is why Members, in imposing trade restrictions, must adduce evidence and evaluation of an actual risk against which their restriction or measure mitigates. The United States and JECFA have conducted risk assessments and concluded that the hormones do not pose a risk to consumers when used as growth promoters in cattle. That is why the United States does not, like the EC, impose a ban on the importation and sale of beef from treated cattle. The EC chooses to ban importation of this same beef. Therefore, the relevant analysis is whether the EC, in support of its provisional ban on meat from cattle treated with these hormones, has adduced sufficient evidence to demonstrate that it has based its provisional ban on available pertinent information and that there is insufficient scientific evidence for the EC to conduct a risk assessment for the hormones. The experts' responses demonstrate generally that the EC has failed to demonstrate either of these elements. The experts' responses to Question 59 specifically indicate that the EC's conclusion that immune or other adverse effects from use of the five hormones as growth promoters in cattle is scientifically baseless.

166. Question 60: Citing to one of its "17 Studies",[158] the EC states that residues of MGA detected in US beef were "much higher than the levels which should have been normally expected." However, the study that the EC refers to does not report actual residue levels in US beef, but is one in a series of studies in which the EC deliberately overdosed cattle with MGA. The EC may have intended to cite to another of its "17 Studies"[159] in which the author reports that measurement of MGA in 103 US beef samples "revealed MGA at trace levels in about 75 percent of the samples." No quantitative data are provided in this report, and there is no suggestion that the "trace levels" were violative according to US tolerance levels. Therefore, the EC has failed to provide any evidence to support its claim that MGA is conducive to misuse or is administered in a manner that would result in unsafe residue levels in US beef.

167. Citing again to one of its "17 Studies"[160] in which a misuse scenario was created for MGA, the EC notes that MGA has a "boosting effect" on residues of estradiol 17β in meat. It is true that this study demonstrated a 2.6-fold increase (not 3-fold as suggested by the EC) in estradiol 17β concentrations in fat following treatment with the FDA-approved dose of MGA. This is not surprising in light of the fact that MGA, at low concentrations, increases ovarian estradiol 17β secretion via effects on hormone negative feedback to the hypothalamus and pituitary gland. However, it should be noted that: (1) the results of this study are preliminary due to the limited number of animals used (only 2-4 animals per treatment group), and (2) the mean concentration of estradiol 17β in fat following MGA treatment (26 ppt) is 19 times lower than the US tolerance (480 ppt).[15161] Again, the evidence put forward by the EC simply fails to substantiate its claim that the use of MGA according to good veterinary practices results in hormone residues above the levels that have been determined to be safe for human consumption.

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

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

[158] Exhibit EC-16.
[159] Exhibit EC-19.
[160] Exhibit EC-16.
[161] *See* 21 C.F.R. § 556.240.

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

170. The EC provides commentary on levels of residues in the event of non-removed implants. The United States has provided lengthy discussion of how implants are injected into the ears of cattle, that those ears are then discarded, and that ante- and post-mortem inspections ensure that the implants are not entering the food chain.[162] The EC's commentary speculates that an ear with an intact implant will enter the food chain. Again, this is nothing more than a paper exercise, and there is no evidence that this event will occur. The EC dismisses Dr. Boobis' response as "unfounded." However, the United States notes that Dr. Boobis has engaged in a detailed review of the materials underpinning the EC's ban, and has based his conclusion on the results of these very materials.[163] The United States reached the same conclusion after review of the scientific materials put forward by the EC.[164]

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

172. The EC questions the "objectivity and impartiality" of the reasoning of Drs. Boobis and Boisseau. The EC's rhetoric regarding the responses of these experts is inappropriate. Rather than citing to evidence that actually supports the EC's stance on these hormones in an attempt to discount the experts' advice, the EC instead seeks to impugn the credibility of the impartial individuals who have agreed to assist the Panel in its endeavours. Rather than a negative, the United States views the fact that Drs. Boisseau and Boobis "have both served on a JECFA panel that examined some of these hormones" as testament to their qualifications, as well as evidence against the EC's refrain that they lack relevant experience in the study of the hormones.

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

> Estradiol 17β: Dr. Boisseau: "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of oestradiol-17β are related to a mechanism other than hormonal activity."[15165] Dr. Boobis: "[t]he carcinogenic effects of oestradiol appear to be a consequence of its endocrine

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

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

[164] *See*, *e.g.*, US Rebuttal Submission, Section II.B.4.

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

activity." Dr. Guttenplan: "an adverse effect cannot be ruled out, but it is unlikely if good veterinary practices are followed." Dr. Cogliano: "it has not been established by the EC that genotoxicity and cell proliferation would be induced by levels found in meat residues added to the pre-existing levels occurring in exposed humans."[166]

Testosterone and progesterone: Dr. Boisseau (regarding both hormones): "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of [either hormone] are related to a mechanism other than hormonal activity."[167] Dr. Guttenplan: "Progesterone, testosterone have been extensively investigated and the assessment seems sound and is based on the no effect level and a safety factor. (JECFA meeting 52, report-WHA TRS 893)." Dr. Boobis: "[t]here is no evidence that the hormones testosterone or progesterone have genotoxic potential."[168]

Zeranol: Dr. Boisseau: "the scientific evidence relied upon in the SCVPH Opinions does not support the conclusion that the carcinogenic effects of zeranol are related to a mechanism other than hormonal activity."[169] Dr. Guttenplan: "[t]here is no conclusive evidence presented by the EC that the five hormones other than oestradiol-17β [*i.e.*, including zeranol], when consumed as residues in meat have genotoxic potential."[170] Dr. Boobis: "[t]here is no convincing evidence that trenbolone acetate, MGA and zeranol are genotoxic. They were negative in a range of tests for genotoxicity ... [t]hus, there is no evidence that any of the hormones are genotoxic in vivo at the levels found in meat from treated animals. Even if GVP were not followed, the levels of exposure to the hormones would be such that no genotoxicity would be anticipated in vivo."[171]

174. The EC complains that Drs. Boobis and Boisseau reached their conclusions despite the fact that "available evidence is insufficient or there are total gaps in our knowledge." Again, the EC presents no evidence in support of this conclusion, and it is a statement with which the experts do not agree.[172]

175. The EC invokes Drs. Sippell, De Brabander and Cogliano, and notes that although "they have not expressed themselves on this precise question" the EC is sure that, had they responded, they would have supported the EC's argument. This is simply conjecture, and it contradicts the EC's earlier objection to experts responding to questions which they had not previously indicated themselves capable of answering.[173]

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

[166] Dr. Cogliano Responses (Question 18), p. 1.
[167] Dr. Boisseau Responses (Question 21), p. 16.
[168] Dr. Boobis Responses (Question 21), p. 24.
[169] Dr. Boisseau Responses (Question 21), p. 16.
[170] Dr. Guttenplan Responses (Question 21), p. 6.
[171] Dr. Boobis Responses (Question 21), p. 24.
[172] *See* US Comments on the Experts' Responses, Section C.3(c).
[173] *See* EC's Comments on the Experts' Responses (Question 2) ("Dr. Boisseau's reply that 'In my e-mail of 26/04/06, I have indicated that I did not think that I am in the position to reply to this question' calls into question the reliability of his answer to question no 1 and indeed to the other questions.)

insufficiencies and contradictions in the scientific information used by JECFA for conducting its risk assessments."

177. The EC complains of Dr. Boobis' lack of "any specific expertise" and claims to have clarified Dr. Boobis' responses on the basis of " a more careful examination by a real expert." The EC's rhetoric is inappropriate and misplaced. The purpose of this exercise is not to have the EC rewrite the responses of the experts whose assistance the Panel has solicited with the opinions of "real experts" assisting the EC in arguing this dispute. This would defeat the entire purpose of the Panel's seeking advice from an impartial group of experts in order to make sense of the technical arguments raised by the parties. The United States has provided a detailed argument of why the Leffers study reviewed by the EC's "expert" does not stand for the proposition the EC contends it does.[174] Dr. Boobis concludes the following regarding alleged gaps in the scientific information:

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

178. The EC agrees with Dr. Guttenplan, who it contends "provides some examples of the areas in which gaps and uncertainties have been identified and indicates some of the additional research that is required before the EC would be able to conduct a more complete risk assessment." The EC's endorsement of Dr. Guttenplan's response is ironic since the majority of the purported gaps identified in his response relate to estradiol 17β, the hormone for which the EC claims to have conducted a risk assessment within the meaning of Article 5.1 of the SPS Agreement.[175] If, as the EC appears to contend in its comments, there are substantial gaps in this data, it is unclear how the EC can justify a permanent ban on its use. The United States notes the following comments from Dr. Guttenplan regarding the provisionally banned hormones, for which the EC claims substantial gaps in the scientific data:

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

[174] *See* US Comments on the Experts' Responses, paras. 79-80.
[175] *See* EC First Written Submission, para. 17.

estrogenic studies have been carried out. Actual levels in beef were not provided. (JECFA 62 FNP 41/16)."[176]

D. CONCLUSION

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

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