

**CANADA – 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/DS321/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**

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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-17 β , 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 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. 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 medicine 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 Communities 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-17 β , 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-17 β 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-17 β 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: *17 β -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 endocrine 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 17 β -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-17 β 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-17 β , 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-17 β 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 or 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 discuss 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-17 β 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-17 β 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-17 β is associated with its hormonal activity, when JECFA itself was more cautious when stating that "the carcinogenicity of oestradiol-17 β 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-17 β 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- α 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-17 β 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-17 β 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-17 β to pre-pubertal girls to changes in growth pattern despite the fact that serum levels of oestradiol-17 β 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-17 β 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-17 β ?

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-17 β 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-17 β 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-17 β , 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-17 β 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-17 β . 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-17 β 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-17 β , 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-17 β) 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 17 β -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 17 β -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 17 β -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-17 β 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-17 β 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-17 β 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-17 β 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-17 β 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-17 β 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-17 β , 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 17 β , 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-17 β 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 restraint 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 17 β . 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 synthesised (prepared) from plant material and that in plant material the $^{13}\text{C}/^{12}\text{C}$ ratio is different from the $^{13}\text{C}/^{12}\text{C}$ ratio of animals. Equally, the finding that the residues of the endogenously produced natural hormones in cattle are in the 17 α form (inactive) while the use of the natural hormones for growth promotion purposes may lead to residues in the β 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-17 β 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-17 β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." 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 as "... 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 were 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 disclose 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 than 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 17 β -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 17 β -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-17 β 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 17 β -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-17 β ? 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-17 β ? [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-17 β is inactive orally". This is simply factually wrong! Oestradiol-17 β is routinely administered 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 administered 8 μ g conjugated oestradiol-17 β in the form of encapsulated powder. Moreover, in the "benchmark study" on oestradiol-17 β performed in rats (Cook et al., 1998) the rats were orally dosed with oestradiol-17 β . Thus, there are no doubts that oestradiol-17 β 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 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 is 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-17 β 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 a 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-17 β 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 meat 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-17 β 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 17 β , 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 quantitative) 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-17 β 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-17 β 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, JECFA 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 were 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 does 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 it 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-17 β [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 oestradiol-17 β [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-17 β [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-17 β [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 meat 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-17 β 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 μ g/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-17 β 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 untreated 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-17 β , 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-17 β , 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 oestradiol-17 β) "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 data, 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-17 β , Dr. Boisseau expressly states that "in its 32nd session held in 1987, JECFA did not address this kind of non-linear situation for oestradiol-17 β (...)". 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 submission⁴ 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-17 β 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 17 β , 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-17 β " 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 17 β and its catechol metabolites in animal and human tissue as well as the mutagenicity of oestradiol 17 β 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 17 β 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-17 β 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-17 β ?

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-17 β 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-17 β . 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 17 β " 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-17 β (...) 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-17 β as a human carcinogen indicates that there are potential adverse effects on human health when oestradiol-17 β 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-17 β 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-17 β 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-17 β as determined in cell culture. For example, Kong et al (*Int. J. Oncology*, 17: 1141-1149, 2000) reported on the mutagenicity of oestradiol-17 β 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-17 β in BB Rat2 embryonic cells. In this study, multiple treatment of the cells with 50 to 200nM 4-OH oestradiol-17 β 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-17 β 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-17 β 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-17 β 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-17 β 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 adenine 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-17 β 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 17 β and its catechol metabolites in animal and human tissue as well as the mutagenicity of oestradiol 17 β 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 17 β 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-17 β 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 17 β 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 17 β 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 17 β 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 17 β . 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 than 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 17 β 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 17 β 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-17 β) 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 17 β 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 "concur[s] [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 17 β 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 17 β 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-17 β , 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 one's 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 vein, 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-17 β 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-17 β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." 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-17 β 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:

"Treatment 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-17 β 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 " $0+0 \approx 0$ " (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 Xenooestrogens 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 is 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 than 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-17 β ? 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-17 β ? [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 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), 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 17 β 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 17 β 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 bioavailability 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-17 β 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-17 β 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 17 β 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 17 β 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 17 β . 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 17 β 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 \approx 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-17 β 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, progesterin receptor and glucocorticoid receptor. This was not documented before. Dr. Boobis and certainly the US (at para. 49) in their statements still call trenbolone 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 progesterin 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 17 β 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 Zeranone (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- α . 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 adenine 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 17 β)

ANNEX F-4

**COMMENTS BY CANADA TO THE REPLIES
OF SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC
TO QUESTIONS POSED BY THE PANEL**

(30 June 2006)

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I. INTRODUCTION

1. Canada is pleased to have this opportunity to comment on the responses to the Panel's questions of the experts and international organizations. Canada expresses its appreciation to the experts and international organizations for having agreed to participate in this proceeding as scientific and technical advisors to the Panel.

2. The Panel has sought advice on the scientific and technical matters that arise in the context of the dispute between the parties over whether the European Communities (EC) has complied with the recommendations and rulings of the WTO Dispute Settlement Body (DSB) in *EC – Measures Concerning Meat and Meat Products (Hormones)*. In light of the nature of this dispute, the most relevant questions (and answers) are those that shed light on whether the scientific evidence relied upon by the EC supports its conclusions that there is a potential for the occurrence of adverse effects from the consumption of meat from cattle that have been treated with oestradiol 17 β , and that there is insufficient scientific evidence to conduct an assessment of the risks from consuming meat from cattle that has been treated by any of the other five hormone growth promoters (HGP).

3. The responses provided by the experts and international organizations generally confirm the explanations of the scientific and technical issues provided by Canada in its previous submissions.¹ With some limited exceptions, these responses indicate that (1) the EC's regulatory opinions do not properly evaluate the potential for adverse effects to human health from residues of oestradiol 17 β in meat from cattle treated when used for growth promotion, and (2) that the available scientific evidence is sufficient to conduct an assessment of the risks from consuming meat that has been treated with any of the remaining five HGP.

4. The issues are complex, however, and Canada submits these comments with a view to further assisting the Panel in understanding these matters. Canada has sought to identify where the experts and international organizations agree with one another and with Canada's explanations of the scientific and technical issues, to reconcile any inconsistencies among the responses received, to elaborate on certain responses that require clarification or amplification, and to address advice by certain experts that is not supported by the available scientific evidence. In several instances, Canada suggests follow-up questions that the Panel may consider asking the experts at a later date.

II. COMMENTS ON THE RESPONSES FROM THE EXPERTS

A. GENERAL DEFINITIONS

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

5. Canada has no comment on the responses to this question provided by Drs. Boisseau, Boobis and Guttenplan other than to note that there does not appear to be any material disagreement concerning these terms.

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.

6. Drs. Boobis and Guttenplan provide definitions of the terms identified by the Panel. While the responses appear to be consistent, Dr. Boobis' reply is more thorough and supported by references.

7. A few key definitions warrant highlighting. According to Dr. Boobis, carcinogenicity is the "[p]rocess of induction of malignant neoplasms", or what is commonly referred to as cancer. Neoplasms, which are new and abnormal formation of tissue, can be malignant or benign. Malignant neoplasms (cancer) pose the greatest risk to human health. In contrast, mutagenicity is the "[a]bility of a physical, chemical or biological agent to induce heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof)." Mutagenicity does not necessarily lead to the formation of malignant neoplasms (cancer).

8. Genotoxicity is the "[a]bility to cause genetic damage." Genotoxicity does not necessarily lead to mutagenicity, if the damage to the DNA is not inherited into the genotype of the affected cell. Genotoxic potential means that a compound "possesses characteristics such that it might be capable of causing genotoxicity (usually *in vivo*), based on considerations such as the results of tests *in vitro*."

¹ Canada First Written Submission, at paras. 86-131; Canada First Oral Statement, at paras. 41-73; and Canada Rebuttal Submission, at paras. 45-146.

Dr. Boobis emphasizes that "[i]t remains to be determined whether genotoxicity is indeed expressed *in vivo*, i.e. that the potential is realized". Thus, "potential" does not refer to the statistical likelihood that the genotoxic mode of action will occur *in vivo*, but, rather that the genotoxic mode of action is theoretically possible.

9. Combining these concepts, if a compound is only identified as having genotoxic potential, the compound is still several steps removed from carcinogenicity. The genotoxic potential will have to be realized *in vivo*, the genetic damage to the cell would have to be "fixed" into the genome created a mutated cell, the mutated cell in turn would have to replicate to form neoplasms, and the neoplasm would have to be malignant (cancer). Any one of these steps may be thwarted by the various effective and redundant defence and repair mechanisms.²

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.

10. This question was also posed to the international bodies (Question 3). Drs. Boisseau and Boobis, as well as JECFA and Codex, responded.

11. Dr. Boobis, JECFA and Codex identify a significant number of relevant international guidance documents. A review of this documentation indicates that the development of risk assessment techniques by international organizations has been ongoing for decades. The International Program on Chemical Safety (a collaborative venture between the World Health Organization, the United Nations Environment Programme and the International Labour Organisation), as early as 1987, published a comprehensive guidance document entitled *Principles for the Safety Assessment of Food Additives and Contaminants in Food, Environmental Health Criteria 70* (EHC 70).³ EHC 70 sets out principles and approaches to safety assessment for food additives and contaminants, consolidating of 30 years of JECFA experience. While not specific to veterinary drug residues, much of the detailed guidance is relevant to the risk assessment generally, including the assessment of veterinary drugs.

12. Building on EHC 70 and recognizing that the assessment of veterinary drug residues can pose specific issues, the WHO and FAO have issued several guidance documents outlining risk assessment techniques and procedures specific to veterinary drug residues. These include:

- JECFA, *Procedures for Recommending Maximum Residue Limits – Residues of Veterinary Drugs in Food (1987 – 1999)*, (Rome: FAO/WHO, 2000) (JECFA Procedures),⁴
- WHO, *Residues of veterinary drugs in food – WHO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives* (Geneva: January 2001);⁵

² For a clear explanation of the relationship between genotoxic potential and carcinogenicity, see Dr. Boobis' answer to Question 19.

³ The International Program on Chemical Safety, *Principles for the Safety Assessment of Food Additives and Contaminants in Food*, Environmental Health Criteria 70 (Geneva: WHO, 1987); online: <http://www.inchem.org/documents/ehc/ehc/ehc70.htm> (Exhibit CDA-43).

⁴ Exhibit CDA-44 ("*JECFA Procedures for Recommending Maximum Residue Limits*").

⁵ Attached to JECFA's answers to the Panel's questions.

- WHO, *Residues of veterinary drugs in food – Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives* (Geneva: August 1996);⁶ and
- FAO, *Residues of veterinary drugs in food – FAO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives*, (Rome: September 2002).⁷

13. In addition to the above, Codex also identifies several relevant guidance documents, including the *Statements of principles relating to the role of food safety risk assessment*⁸ and the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius Commission*.⁹

14. The JECFA *Procedures for Recommending Maximum Residue Limits* is a consolidation of JECFA's collective experience developing risk assessment techniques and methodologies for veterinary drugs from 1987 to 1999. This document confirms that many of the general risk assessment techniques and methodologies developed by international organizations are also relevant to the risk assessment of veterinary drugs.¹⁰

15. As JECFA points out in its response to Question 3, there is a continuous effort to update and harmonize international level risk assessment techniques for chemicals. However, the fact alone that international risk assessment techniques are continuously subject to refinement and elaboration does not, *a priori*, suggest that existing international techniques and methodologies are inadequate or problematic.

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)].

16. The experts confirm the accuracy of the EC's statement referred to in the Panel's question. However, while the statement is technically correct, the experts confirm that the absence of a Codex standard does not imply an absence of internationally developed risk assessment guidelines or principles. Furthermore, the experts confirm that JECFA based its risk assessment of the hormones at issue on relevant international risk assessment methodologies and techniques.

17. Specifically, Dr. Boisseau states in his reply that:

In the conduct of its risk assessment with respect to the hormones at issue, as for all the other pharmacologically active substances used in veterinary medicine, JECFA has followed the general rationale used by all the countries which have assessed the safety of veterinary drug residues. This rationale has been internationally harmonised through scientific conferences and it is possible to say that there was an international non written agreement on this rationale.

⁶ Exhibit CDA-45.

⁷ Attached to JECFA's answers to the Panel's questions.

⁸ Quoted in the answer by Codex to Question 3 addressed to the international bodies; reproduced in the *Procedural Manual of the Codex Alimentarius Commission* (15th edition), at p. 161.

⁹ Annex 6 to the answers by Codex.

¹⁰ For example, a significant portion of the general toxicological data requirements that have been established for food additives and contaminants are equally applicable to veterinary drug residues. JECFA, *Procedures for Recommending Maximum Residue Limits*, at p. 3 (Exhibit CDA-44).

18. Referring to the documents identified in his response to Question 3, Dr. Boobis also confirms that JECFA relied upon a number of relevant guidance documents in its risk assessments of the hormones at issue. Moreover, Dr. Guttenplan acknowledges that the "principles for risk assessment...were used in determining Acceptable Daily Intakes (ADI) for estradiol, progesterone, and testosterone."

19. It is apparent from the experts' answers that international organizations have expended considerable effort in developing risk assessment techniques relevant to the assessment of veterinary drugs. Much of that effort has been the result of contributions from the EC's own Member States¹¹ and much of the resulting guidance used as a basis for decisions taken by European regulatory authorities, including the Committee for Veterinary Medicinal Products (CVMP). Thus, 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.

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

20. The responses of all four experts who replied to this question appear to be consistent with the response provided by Codex to a similar question posed to the international bodies (Question 5). In all cases, the experts and Codex identify a functional separation between risk assessment and risk management. In the context of food safety, a risk assessment is a scientific process in which data are evaluated and on this basis, together with the weight of evidence and expert judgment, a conclusion is reached as to the nature of the hazards, the potential risk to exposed individuals and the extent to which exposure is within those levels considered to be without appreciable risk.¹² The descriptions of risk assessment provided by the experts are consistent with the definition of risk assessment set out in Annex A(4) of the *SPS Agreement*, namely an evaluation of the potential for adverse effects on human health.

21. Risk management, on the other hand, is the process of weighing policy alternatives, considering the risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.¹³ This description of risk management is akin to the process of identifying and selecting SPS measures appropriate to the circumstances.

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.

22. This question is the same as Question 6 addressed to the international bodies. Drs. Boisseau, Boobis and Guttenplan, as well as JECFA and Codex, respond to this question. Their answers reflect principles for the conduct of a risk assessment generally accepted by the international community.

Hazard Identification

23. With slight differences, the experts and international bodies appear to agree that hazard identification involves the determination of whether an agent has the potential to cause adverse effects.

¹¹ For instance, the UK Department of Health and Social Security was instrumental in providing support for EHC 70.

¹² See *e.g.* Dr. Boobis, at p. 12.

¹³ Codex, at p. 6.

Hazard Characterization

24. Again, with slight differences, the experts appear to agree that hazard characterization involves the quantitative and/or qualitative evaluation of the nature of the identified adverse effects caused by the agent. The experts agree that, where possible, hazard characterization should involve a dose-response assessment and a determination of whether a threshold can be established below which no adverse effects can be expected to occur.¹⁴ The outcome of this step is the establishment of a No-Observed-Adverse-Effects-Level (NOAEL), from which an Acceptable Daily Intake (ADI) is derived. The experts' answers are consistent with JECFA's response that "[d]ose-response assessment is an integral part of each assessment and is an essential part of the hazard characterization step." As Canada has stated previously, central to this dispute is whether the EC's failure to complete this "integral part" of the risk assessment implies that the assessment conducted by the EC fails to meet the requirements of the *SPS Agreement*.¹⁵

Exposure Assessment

25. In terms of exposure assessment, the experts confirm that the objective of this step is to evaluate quantitatively exposure by relevant population groups to the substance under review. In order to do so, risk assessors typically use a "food basket" which is based on "available intake data at the upper limit of the range for individual consumption of edible tissues and animal products".¹⁶ The "food basket" used by JECFA is as follows:

Muscle	300 g
Liver	100 g
Kidney	50 g
Tissue Fat	50 g
Milk	1.5 litre
Eggs	100 g

26. The Panel may wish to seek clarification from the experts on whether the food basket is adjusted to reflect estimated consumption by prepubertal populations.

Risk Characterization

27. The experts all appear to agree with the Codex definition of risk characterization: a qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on the three preceding three steps of a risk assessment. Dr. Boisseau specifies that:

... the goal of the risk analysis for these compounds is not to assess qualitatively and quantitatively the likelihood and the gravity of the adverse effects for the health of consumers associated with the veterinary drug residues they are exposed to through the animal derived food[,] but to protect consumers' health from any adverse effect associated with these residues. [emphasis added]

¹⁴ Dr. Boisseau, at p. 5; Dr. Boobis, at p. 13.

¹⁵ Canada Rebuttal Submission, at para. 78.

¹⁶ JECFA, *Procedures for Recommending Maximum Residue Limits*, at p. 31 (Exhibit CDA-44). Also see JECFA, *Evaluation of certain veterinary drug residues in food: Fifty-second Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 893 (Geneva: WHO, 2000), at p. 67 (Exhibit CDA-16).

28. The experts confirm that to achieve the goal of no adverse effects on human health, Maximum Residue Limits (MRL) are established. The purpose of the MRL is to ensure that the exposure to residues of the veterinary drug in question consumed in edible animal products does not exceed the ADI established for that drug.

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]

29. The same question was put to the international bodies (Question 7). JECFA, Drs. Boobis and Boisseau respond. 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.

30. The assumption implicit in the EC's statement is that, in non-linear situations, no threshold can be established below which there is no appreciable risk. As the experts and JECFA point out, this is simply not true. JECFA explains that "probabilistic or deterministic approaches can be applied, independent [of whether] a compound is assumed to act via a threshold mechanism, i.e. non-linear" and "non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect." Thus the important issue is not linearity, as the EC has asserted, but rather whether a threshold mechanism operates and an ADI can be set. In deciphering the EC's logic, Dr. Boobis states that the EC's assertion presupposes a specific outcome to the risk assessment, *i.e.*, that no threshold can be set below which no adverse effects occur. This is simply not true. JECFA explains that "[i]n such a case, as for the hormones, a no-effect-level can be determined from which an ADI can be established."

31. In support of its "non-linearity" claim, the EC argues that "here, the risks are embedded in changes in exposure to biologically active molecules which may, within minute differences in their bioavailability, have dramatic effects, such as turning on or off complete developmental programs of the human genome, or inducing pathological conditions."¹⁷ The EC presents no evidence that the minute increases in exposure to the hormones resulting from residues of growth promoting hormones in treated meat "turn[] on or off complete developmental programs of the human genome, or induc[e] pathological conditions." This is not surprising given that wide variation in background levels of hormones endogenously produced by humans and considerable exposure to dietary sources of hormones.

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.

32. This question is the same as Question 10 addressed to the international bodies. The description provided by the experts of the procedure followed by JECFA in the identification of ADIs and development of recommendations on MRLs appears to be consistent with JECFA's answer to Question 10. In terms of the steps taken in the risk assessment process to build in a margin of safety, Dr. Boobis describes similar steps in his answer to Question 12 when addressing scientific uncertainty. Canada would like to highlight the following:

¹⁷ EC Replies to Questions from the Panel, Question 24. at para. 140. The EC refers to no scientific evidence in support of this assertion.

Establishment of ADI

33. The experts and JECFA have confirmed that the ADI is the highest quantity of residue that can be ingested on a daily basis over a lifetime that will not result in adverse effects to health, or, as Dr. Boobis states in response to a later question, that will pose zero risk.¹⁸ The establishment of the ADI is a two-step process involving the determination of a NOAEL and the application of safety factors.¹⁹ A NOAEL is established for each adverse effect. The NOAEL from the most sensitive adverse effect is used as the NOAEL for the substance.²⁰ "Safety factors" are applied to the NOAEL to take into account inherent uncertainties in extrapolating animal toxicity data to potential effects in human beings and variation in the human species.²¹ The experts and JECFA confirm that JECFA typically uses a default safety factor of 100, representing a safety factor of 10 for extrapolation from animal to human species and a safety factor of 10 for diversity within the human population. Smaller safety factors may be justified in certain circumstances, such as where the NOAEL is derived from data from human studies. Extra factors may be applied in other circumstances such as where there is an identifiable sub-group that might reasonably be expected to be more sensitive than the group in which data were obtained (e.g., children relative to adults).²²

34. In the case of the six hormones at issue, JECFA has established the following ADIs:

Hormone	JECFA Meeting	Exhibit #	Pg.	ADI	Safety Factor
Oestradiol 17 β	52 nd Meeting	CDA-17	60	0-0.05 μ g/kg	100
Progesterone	52 nd Meeting	CDA-17	62	0-30 μ g/kg	100
Testosterone	52 nd Meeting	CDA-17	64	0-2 μ g/kg	1000
Trenbolone Acetate	34 th Meeting	CDA-30	107	0-0.02 μ g/kg	100
Zeranol	32 nd Meeting	CDA-29	145	0-0.5 μ g/kg	100
Melengestrol Acetate	54 th Meeting	CDA-31	179	0-0.03 μ g/kg	200

Proposal of an MRL

35. The experts have confirmed that the MRL is a risk management tool designed to ensure that exposure to veterinary drug residues does not exceed the established ADI. In other words, 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.

36. The experts and JECFA have set out various ways in which a margin of safety is built into the establishment of the MRL. In this regard, the risk assessor makes the following conservative assumptions:

- the parent substance and all its metabolites have the same potential toxicity unless demonstrated otherwise;²³
- the parent substance and all its metabolites are considered to be bioavailable (or biologically active) unless demonstrated otherwise;²⁴ and

¹⁸ Dr. Boobis, answer to Question 54.

¹⁹ JECFA's answer to Question 10, at p. 6.

²⁰ Dr. Boobis, at p. 15.

²¹ JECFA's answer to Question 10, at p. 6.

²² Dr. Boobis, at pp. 14-15.

²³ Dr. Boisseau's answer to Question 13(B), at p. 10.

²⁴ Dr. Boisseau, at p. 23; Dr. Boobis, at pp. 14-15.

- the standard food consumption figures (the "food basket"), used to estimate exposure, overestimate actual consumption.²⁵

37. As can be observed from the foregoing, JECFA has developed risk assessment techniques that build into its risk assessments a significant margin of safety.

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]

38. The same question was put to the international bodies as Question 11. JECFA states in its response that "[i]f there are substantial data gaps and important information missing, JECFA can not establish an ADI." [emphasis added] This confirms Canada's statement quoted in the question was correct. Thus, given that JECFA established ADI for all six hormones at issue, it is reasonable to infer that the record was complete and sufficient for all hormones in question.

39. The experts who responded to this question, Dr. Boisseau and Dr. Boobis, confirm that Canada's statement is correct as a general rule. Dr. Boobis identified a number of exceptions in which JECFA might issue an ADI without a complete dataset. As he explains, the "critical issue is whether a sufficiently cautious default can be adopted in the absence of certain information." He concludes that "JECFA would require a complete data base unless it could adopt default assumptions that would if anything lead to a more conservative risk assessment than would be the case otherwise".

Q10. In paras. 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?

40. The same question was put to the international bodies as Question 12. JECFA's answer clarifies that its role is to conduct risk assessments. It will only consider the health impact of specific risk management options, if requested to do so by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). The response by Codex to Question 12 indicates that it is not necessarily limited to the three risk management options listed in the question, and mentions the possibility of developing "codes of practice" through the CCRVDF.

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]

41. The experts with specific expertise on risk assessments of veterinary drugs explain that a qualitative risk assessment may be conducted under certain limited circumstances. Both Dr. Boisseau and Dr. Boobis agree that a qualitative risk assessment should comprise the main steps of a conventional risk assessment, including hazard identification, hazard characterization and exposure assessment. Both experts also agree that if the mode of action is such that a dose-response relationship cannot be established and, thus, no safe intake threshold can be set, then a quantitative dose-response assessment is not necessary. However, Dr. Boobis explains that even where the need for detailed dose-response analysis would be questionable, a risk assessment still needs "scientific rigour", a

²⁵ Dr. Boisseau, at p. 7.

statement supported by the Appellate Body's description of the risk assessment process as characterized by "systematic, disciplined and objective enquiry and analysis."²⁶

42. Dr. Boisseau provides examples of where JECFA has based its conclusions on a qualitative risk assessment and declined to recommend an ADI (*e.g.*, chloramphenicol and nitroimidazole). Both Dr. Boisseau and Dr. Boobis also confirm in subsequent answers that, in respect of the hormones at issue in this dispute, a dose-response assessment can be undertaken and a safe threshold (ADI) can be established for each hormone.²⁷ Thus, it can be inferred that, according to internationally developed risk assessment techniques, a risk assessment for these substances that does not include a dose-response assessment would be incomplete.

43. Dr. Cogliano also responds to this question with references to IARC's practice in developing its monographs. However, the type of assessment to which Dr. Cogliano refers only satisfies the first element of a risk assessment contemplated by the *SPS Agreement*, which includes both the identification of adverse effects arising from the substance at issue and the evaluation of the potential of occurrence of such effects. In this regard, it is important to recall the Appellate Body's conclusion regarding previous IARC Monographs relied upon by the EC in the first hormones dispute. After citing the Panel's conclusion that the IARC Monographs were "in the nature of general studies of...the carcinogenic potential of the named hormones" and have not "evaluated the carcinogenic potential of those hormones when used specifically *for growth promotion purposes*"²⁸, the Appellate Body, in *EC – Hormones*, concluded as follows:

We believe that the above findings of the Panel are justified. The 1987 IARC Monographs and the articles and opinions of individual scientists submitted by the European Communities constitute general studies which do indeed show the existence of a general risk of cancer; but they do not focus on and do not address the particular kind of risk here at stake – the carcinogenic or genotoxic potential of the residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes – as is required by paragraph 4 of Annex A of the *SPS Agreement*. Those general studies, are in other words, relevant but do not appear to be sufficiently specific to the case at hand.²⁹

44. It is also worth noting that Codex has estimated general principles in relation to the use of quantitative information. For instance, the *Codex Statements of principles relating to the role of food safety risk assessment* include requirements that "[f]ood safety risk assessment should be soundly based on science, ... ", and that "[r]isk assessment should use available quantitative information to the greatest extent possible ..." [emphasis added] Moreover, paragraph 20 of the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* restates the same principles while recognizing that a risk assessment may also take into account qualitative information. Paragraph 23 of the *Working Principles* also provides:

Constraints, uncertainties and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner. Expression of uncertainty or variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable. [emphasis added]

²⁶ *EC – Measures Concerning Meat and Meat Products (Hormones)*, Report of the Appellate Body, WT/DS26/AB/R, WT/DS48/AB/R, adopted February 13, 1998, at para. 187 (*EC – Hormones*).

²⁷ See answers to Questions 36 and 37.

²⁸ *EC – Hormones*, Report of the Appellate Body, at para. 199.

²⁹ *Ibid.*, at para. 200.

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?

45. Both Drs. Boisseau and Boobis explain the numerous ways in which scientific uncertainty is addressed in a risk assessment. Dr. Boobis' response is worth quoting at length:

One way of dealing with uncertainty is [1] to default to the worst case in the absence of evidence to the contrary. Hence, the most sensitive relevant endpoint in the most sensitive species is used as the basis of the risk assessment. [2] In extrapolating to humans a default factor of 10 is used to allow for species differences, which assumes that humans are more sensitive than the experimental species. [3] A further factor of 10 is included for interindividual differences. These differences may be due to gender, genetics, life stage or other factors. [4] However, to some extent such differences have already been taken into account in the choice of endpoint, as this will usually represent the most sensitive lifestage, gender and to some extent genetics by using data from the most sensitive species. [5] Where there are additional uncertainties, such as no NOEL or the absence of a non-critical study, an additional safety factor will be included, and this is almost always conservative, as when the data gaps have been completed, the appropriate safety factor is almost always less than that used to account for these data gaps. [6] The residue may be assumed to be all as active as the most active moiety, which is almost always a conservative assumption. [7] Dietary intake is based on conservative data for food consumption. [8] It is also assumed that all meat that could contain veterinary drug residue will contain the residue and that this will be present at the high end of the range (MRL or other appropriate level). [9] In respect of the ADI, the assumption is that intake will be at this high level for a lifetime, when in reality there will be occasions when little or no meat is consumed or that which is consumed contains less or even no residue. In their risk assessment of the hormones, JECFA applied all of these approaches to dealing with the uncertainty.

46. Dr. Boisseau indicates that the EC "did not consider any scientific uncertainty", because it had decided as a matter of "principle" that it was not possible to establish an ADI for genotoxic substances. Clearly, however, this "principle" is one of selective rather than general application, if one considers that the EC knowingly allows its population to consume, without so much as a warning, the very same "genotoxic" substance (*i.e.*, oestradiol 17 β) naturally present in many dietary sources (*e.g.*, milk, eggs, meat) and in oral contraceptives, at levels many times higher than that which would be present as residues of growth promotants.

B. 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 17 β 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?

47. Drs. Boisseau, Boobis and Guttenplan chose to answer this question, and all of them indicate that the EC's "risk assessment" (*i.e.*, the three SCVPH opinions) was deficient in one manner or

another in its evaluation of the potential occurrence of adverse effects (whether carcinogenic, genotoxic or other) from the consumption of residues of oestradiol 17 β in meat from treated animals.

48. Dr. Boisseau acknowledges the general international agreement that oestradiol 17 β is associated with "carcinogenic potential", but also confirms what Canada has explained in its submissions: that this potential is due to the hormonal effect of estrogens,³⁰ which requires "prolonged exposure to high concentrations" for adverse effects to occur. Exposure to residues of these hormones from meat from treated cattle does not generate the "high concentrations" considered by Dr. Boisseau and others to be required for these effects to occur.

49. Dr. Boisseau further confirms that, despite the growing acknowledgement that oestradiol 17 β may have "genotoxic potential", there is no evidence that this potential is realized *in vivo* (as opposed to *in vitro*). He points out that, as a result of what must be done to observe a genotoxic effect (*i.e.*, use far higher than realistic doses of the parent compound with an assumption that the toxicity is the same as that for residues), such tests are more useful for identifying modes of action than for assessing dose-response relationships. He therefore disagrees with the EC, as do most other experts and international scientific bodies, that no threshold can be set for substances for which "genotoxic potential" has been identified.

50. Dr. Boisseau also shares Canada's concern that the EC did not conduct any "quantitative risk assessment" of other adverse effects, known to be dose-dependent, that would lead to the establishment of thresholds and ADIs that would differ from those established by JECFA. The quantitative assessment referred to here is not the same as that contemplated by the Appellate Body when it found that a risk assessment need not quantify the risk.³¹ Rather, Dr. Boisseau refers to analyses of the dose-response relationship that is completely absent from the EC's opinions, but which is a crucial component of internationally accepted risk assessment techniques and is essential if the EC is to demonstrate that existing international standards are insufficient to achieve its appropriate level of protection.

51. Dr. Boobis also cites the flaws in the EC opinions as a risk assessment, in particular that the analysis "focused primarily on hazard identification". He confirms what Canada has explained in its submission,³² that there was "little in the way of hazard characterization and no independent exposure assessment". Without the data generated in these steps, which have been shown in responses to previous questions to be necessary components of a risk assessment, Dr. Boobis advises the Panel that "it was not possible [for the EC] to complete the risk characterization phase". Most importantly, Dr. Boobis indicates that the EC "essentially stopped" the assessment of risk after it concluded that no thresholds of exposure could be established. In light of the later responses of all the experts about the issue of thresholds,³³ this observation by Dr. Boobis is critical: it means that the EC decision not to conduct a complete risk assessment was based on a conclusion that is not supported by the evidence.

52. For his part, Dr. Guttenplan similarly finds that the EC's evaluation of the potential occurrence of adverse effects is "weak", even as he accepts that the EC did identify potential adverse effects. However, identifying potential adverse effects (*i.e.*, the hazard identification) is only the starting point of a valid risk assessment. As for the remaining components of such an assessment, Dr. Guttenplan points to several deficiencies in the EC's opinions (*i.e.*, limited utility of animal models, absence of epidemiological studies, *etc.*) and concludes that "little can be inferred about the potential occurrence of the adverse effects".

³⁰ Canada First Written Submission, at paras. 95-97; Canada Rebuttal Submission, at paras. 90-96.

³¹ *EC – Hormones*, Report of the Appellate Body, at paras. 186-187.

³² Canada Rebuttal Submission, at paras. 76-85.

³³ See Canada's comments below on the experts' responses to questions 16-19.

Q14. In your view, does the risk assessment undertaken by the European Communities on oestradiol 17 β 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 17 β ?

53. In addition to their responses to the more general question above, Drs. Boisseau, Boobis and Guttenplan also agree with Canada that the EC failed to follow the Codex guidelines on risk assessments. The experts share Canada's concerns that the EC (and SCVPH) took significant and unjustified short-cuts in the conduct of its risk assessment.³⁴

54. Dr. Boisseau is very critical of the EC's decision not to follow the Codex guidelines, concluding that the EC's own science did not justify the abandonment of these guidelines. At most, Dr. Boisseau concedes that the scientific studies relied upon by the EC indicate that it should have refined its approach to assessing exposure to hormone residues, not abandon the entire risk assessment methodology. But as Canada has indicated in its submissions,³⁵ the EC has done very little that resembles an exposure assessment.

55. Dr. Boobis states simply that the EC did not follow Codex guidelines (which include the four steps), adding that even if the EC concluded that oestradiol 17 β was genotoxic – a conclusion with which Dr. Boobis disagrees in his response to Questions 15, 18 and 19 – the EC should still have followed all four steps.

56. Dr. Guttenplan also finds it difficult to give the EC's risk assessment anything more positive than a "mixed rating". For many of the same reasons advanced by the others, Dr. Guttenplan finds fault in the EC's hazard characterization and risk characterization, the first because of the questionable relevance of studying hamster kidneys for the task at hand and the second because it is "qualitative at best", and not based on any data or confirmed by epidemiological studies. Moreover, Dr. Guttenplan's limited support for the EC's exposure assessment is left unexplained; he simply declares it to be "thorough", which is itself an odd declaration in light of the EC's own admission that it did not, because it could not, conduct an exposure assessment.³⁶

C. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

Q15. Does the identification of oestradiol 17 β 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]

57. Drs. Boisseau, Boobis and Guttenplan all agree with Canada that the mere identification of oestradiol 17 β as a carcinogen is not itself sufficient to conclude that there are potential adverse effects when consumed as residues in meat from treated animals. Not only is the evidence of the substance's carcinogenicity in general not indicative of carcinogenicity of the substance from a given source, but 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 17 β .

³⁴ Canada Rebuttal Submission, at para. 86.

³⁵ *Ibid.*, at paras. 83-85.

³⁶ EC Rebuttal Submission, at para. 141; 1999 SCVPH Opinion, at p. 20 (Exhibit CDA-2).

58. The experts arrive at this conclusion following the tried and tested methods of the international scientific community. Dr. Boobis' explains the relationship between findings of carcinogenicity in general and adverse effects from this one source in particular by stating that "the entire basis of risk assessment in [*sic*] based on the fact that there is a relationship between dose and effect"; and second, that a "key consideration in the risk assessment is whether there is a threshold in the dose-response". Applying these two principles to oestradiol 17 β , which is naturally produced in the human body, Dr. Boobis considers that the main task is to determine whether the additional exposure to hormones from meat from treated animals changes the circulating levels of the hormone. The answer given by JECFA (and not contradicted by the EC) is that it does not; therefore, even though oestradiol 17 β is considered a human carcinogen when exposure is prolonged and significantly greater than the ADI, exposure to it from this single source does not present such risks.

59. The experts do not agree on whether the answer would be different if good veterinary practice (GVP) was not followed. On the one hand, Drs. Boisseau and Guttenplan indicate that there might be a potential for adverse effects if GVP were not followed. As general answers, they are not really surprising. These experts are simply applying a general scientific principle that changes in assumptions in the course of predicting an outcome (*e.g.*, cancer) may change the prediction. While neither expert would guarantee that the outcomes would be the same if GVP had not been followed, they did not state categorically, nor could they have, that the failure to follow GVP will create the potential for adverse effects to occur. In fact, even the studies on this issue submitted by the EC demonstrate that multiple hormone implants resulted in residues that were still less than the ADIs.³⁷

60. Whereas the answers of Drs. Boisseau and Guttenplan are based on general principles about the effect of changing assumptions, Dr. Boobis deals more specifically with the conditions of exposure from the failure to follow GVP. He states that failure to follow GVP would only affect the cancer risk if it resulted in exposure levels above the ADI, and even then it would have to be on a "regular basis". Since he believes that neither of these conditions will be met, Dr. Boobis advises that the failure to follow GVP "would not be associated with any increase in risk of cancer".

61. Dr. Boobis' response suggests an obvious point, but one worth emphasizing: that it is not the conditions under which the hormones are administered that cause adverse effects, but the resulting hormone exposure levels, which depend on many factors. This reinforces the Appellate Body's findings that the EC has to demonstrate through an assessment of the risk arising from the failure to follow GVP that it increases the risk of adverse effects.³⁸ As the advice from the experts confirms, the EC has not done so.

62. For his part, Dr. Cogliano simply asserts, without explanation or support, that the identification of oestradiol 17 β as a human carcinogen indicates consuming it via meat from treated cattle has the potential to cause adverse effects. His answer seems to suggest that he believes there is no threshold below which adverse effects will not occur, a point which he does not support and which is also contrary to the findings of JECFA, Codex and his colleagues who also answered this question. His point that adverse effects depend on the "presence of hormones in the meat that people consume" is also inconsistent with the fact that hormones are already present in meat regardless of whether it is derived from treated cattle or non-treated cattle.

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]

³⁷ Canada Rebuttal Submission, at para. 110 and Exhibit EC-52.

³⁸ EC – Hormones, Report of the Appellate Body, at paras. 205-208.

63. Drs. Boisseau and Boobis agree with Canada that any potential carcinogenic effects of these hormones are related to their hormonal activity, which is dose-dependent and exhibits a threshold exposure level below which these effects will not occur. More importantly, they agreed that the evidence relied upon by the EC does not support the conclusion that adverse effects will arise from anything other than the hormonal activity of these substances, such that existing international standards will be insufficient to meet the EC's level of protection.

64. Dr. Boobis provides extensive analysis of the EC's controversial theory that carcinogenic effects of these hormones may be caused by a mechanism other than hormonal activity, in particular a genotoxic mechanism. Dr. Boobis acknowledges that some studies demonstrate that the hormones may be genotoxic *in vitro*, but categorically rejects, with supporting evidence, that this has been demonstrated *in vivo*. He advises that "guidelines for genotoxicity testing require confirmation of an *in vitro* positive result using an appropriate *in vivo* assay" for such *in vitro* positive result to have any validity. Dr. Boobis provides a number of explanations of why this *in vivo* confirmation is so critical, in particular because the *in vitro* conditions that allow the genotoxicity to be observed do not contain the many defence and repair mechanisms that would exist *in vivo* to prevent cell damage from occurring. The failure to observe positive genotoxicity test results *in vivo* confirms that these defence and repair mechanisms operate to ensure that there is a threshold exposure below which genotoxicity will not occur.

65. Only Dr. Guttenplan attempts to support the EC's conclusion, but he does so with no analysis of his own, choosing instead simply to cite the EC's regulatory opinions. In simply referring to the conclusions of the SCVPH, Dr. Guttenplan has in fact failed to adequately answer the question, which was not whether the SCVPH had concluded that there were non-hormonal adverse effects, but whether the scientific evidence relied upon by the SCVPH supported that conclusion.

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]

66. Drs. Boisseau and Boobis confirm the evidence that catechol metabolites are largely absent in meat from treated animals, and that even if such metabolites were present in small quantities (which they acknowledged may be possible), it would not be enough to make the genotoxic potential of oestradiol 17 β an issue with respect to residues in meat from treated animals.

67. Dr. Boobis advises that the absence of catechol metabolites confirms the effectiveness of the mechanisms for detoxification and elimination of these metabolites *in vivo*. He further confirms that the formation of such metabolites in meat would only be relevant to the risk assessment if it were true that catechol metabolites were responsible for adverse effects and if it were true that there is no threshold for any effects for which they are responsible. In his response to this and other questions, Dr. Boobis advises that neither of these are the case, so the presence or absence of catechol metabolites preformed in meat does "not impact on the risk assessment".

68. Dr. Guttenplan's seemingly contrary acknowledgement that "only very small amounts of catechol metabolites were detected" overstates the case. As other experts confirm in greater detail, the study commissioned by the EC that looked at the issue observed that "no metabolites coming from the catechol oestrogen biosynthesis could be isolated" and that "metabolic studies performed *in vivo* ... and *in vitro*... failed to demonstrate a significant aromatic hydroxylation activity that would lead to catechol oestrogen derived metabolites".³⁹ In other words, contrary to Dr. Guttenplan's claim, catechol

³⁹ Exhibit EC-51A, at p. 18.

metabolites have not been found in meat from treated animals, at least not in detectable quantities, and to the extent that they exist in undetectable quantities, they are not present in sufficient quantities to create a genotoxic potential. In light of the discrepancy between the explicit conclusions of even the EC evidence on this issue and the unsupported claim of Dr. Guttenplan, the Panel may wish to ask him to support his claim.

Q18. Please comment on the US argument that the European Communities fails to demonstrate through scientific evidence that oestradiol 17 β 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]

69. Drs. Boisseau and Boobis both confirm Canada's explanation that the EC has failed to demonstrate that oestradiol 17 β is genotoxic *in vivo*.⁴⁰ They acknowledge what other reputable international scientists and scientific authorities now see as the "genotoxic potential" of oestradiol 17 β , but deny that this "potential" is relevant *in vivo* at doses to which humans are exposed from consuming meat from treated animals.

70. Dr. Boobis reiterates his detailed analysis in response to Question 15 that sets out the many reasons for which genotoxic potential identified in *in vitro* will not be confirmed *in vivo*. In particular, he highlights the important point that the genotoxicity that has been "observed in vitro would be expected to exhibit a threshold." The EC's conclusion that there is no threshold below which genotoxicity will not occur runs directly counter to this advice, and is therefore not supported by the scientific evidence.

71. Dr. Boisseau also highlights an attempt by the EC to misrepresent certain of JECFA's findings. In particular, he points to the EC's efforts to represent JECFA's findings about the "genotoxic potential" of oestradiol 17 β , combined with its decision to establish an ADI, as a finding that oestradiol 17 β is "genotoxic". Dr. Boisseau correctly points out in his answer to Question 13 that there is a difference between a substance having "genotoxic potential" and it being "genotoxic", confirming that JECFA has never considered that oestradiol 17 β is "genotoxic". Dr. Boisseau then explains the rationale behind JECFA's decision to adopt an ADI in 1999, pointing to the need to place exposure to oestradiol 17 β from this source into context. His explanation was confirmed by JECFA in its answer to Question 20. Citing exposure values identified by JECFA, Dr. Boisseau advises the Panel that exposure to residues of the three natural hormones remains a mere fraction of the ADI (conservatively estimated between 0.03% and 4.0%, depending upon the substance). In other words, the EC claims to the contrary notwithstanding,⁴¹ JECFA's establishment of an ADI for the three natural hormones was not related to its findings about "potential genotoxicity". In fact, just the opposite is true: JECFA would not have established ADIs at all if it considered the hormones to be genotoxic *in vivo*.

72. For their part, Drs. Cogliano and Guttenplan both suggest that the EC has demonstrated that oestradiol 17 β is genotoxic, but neither of them does so with reference to supporting scientific evidence. Dr. Cogliano simply repeats the EC's assertion that it is, and endorses an excerpt from the EC Rebuttal Submission that was itself from a report of the UK Veterinary Products Committee

⁴⁰ See Canada First Written Submission, at paras. 95-98; also see Canada Rebuttal Submission, at paras. 86-98.

⁴¹ EC Rebuttal Submission (Canada case), at paras. 100-101.

(VPC).⁴² However, the EC neglected to include, when quoting from that report, the very next paragraph, which concluded that:

[a]lthough there is evidence that oestrogen metabolites may be directly genotoxic *in vitro*, *in vivo* their formation is affected by opposing activation and inactivation metabolic pathways, the presence of anti-oxidants and DNA repair capacity and thus it is likely this genotoxicity will have a thresholded response.⁴³

73. Even as Dr. Cogliano endorses the EC's selective quote from the VPC Report, he also appears to understand and accept the broader context of that quote when he admits 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". This observation brings him in line with Drs. Boisseau and Boobis, who explain that there is a threshold exposure below which genotoxicity will not occur.

Q19. The European Communities states that "... it is generally recognized that for substances which have genotoxic potential (as is the case with oestradiol 17 β) 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]

74. Drs. Boisseau and Boobis (and, to a lesser extent, Dr. Cogliano, but not Dr. Guttenplan) explicitly confirm the main point that Canada has made from the beginning of this dispute: that for substances that are endogenously produced by the human body, there simply must be a threshold below which no adverse effects are observed, or else humanity would have been wiped out by cancer millennia ago. This simple reality, repeatedly ignored by the EC, but stressed time and again by experts from around the world,⁴⁴ contradicts directly the EC's claim about the genotoxicity of the three natural hormones, and its corresponding claim that no threshold can be established.

75. Even though JECFA acknowledged that oestradiol 17 β may have genotoxic potential, it decided to establish an ADI. If there had been no threshold below which exposure to the substance would be safe, JECFA would not have been able to establish an ADI. More recently even, the European Food Safety Authority (EFSA) (the successor to the SCVPH) has recognized thresholds for genotoxic substances when it concluded that, "based on the current understanding of cancer biology there are levels of exposure to substances which are both genotoxic and carcinogenic below which cancer incidence is not increased (biological thresholds in dose-response)".⁴⁵

76. As pointed out by many of the experts in their responses, the consensus among the experts on the issue of thresholds is based not only on their scientific understanding of the modes of action of the

⁴² EC Rebuttal Submission (Canada case) at para. 124. See also UK, Veterinary Products Committee, *Risks Associated with the Use of Hormonal Substances in Food-Producing Animals: Draft report of the UK Veterinary Products Committee*, May 2005 (UK VPC Draft Report), at p. 27 (Exhibit CDA-26).

⁴³ *Ibid.*

⁴⁴ Not only do the experts relied upon by the Panel confirm this, but this conclusion has been confirmed by all international bodies that have addressed the issue. See, for example, VPC and JECFA.

⁴⁵ EFSA, *Opinion of the Scientific Committee on a Request from EFSA Related to a Harmonised Approach for Risk Assessment of Substances which are both Genotoxic and Carcinogenic* (Request No. EFSA-Q-2004-020, adopted October 18, 2005) (*The EFSA Journal*, 282, 1-31, 2005), at p. 18 (Exhibit CDA-46).

substances but also on the absence of any epidemiological studies that demonstrate a relationship between exposure to hormones and adverse health effects.

77. Dr. Cogliano's response does not directly address the question. He offers his view that the difference between the parties to the dispute is simply one of differing assumptions about the nature of genotoxic mechanisms. But the question is not about what Canada or even the EC assume about genotoxic mechanisms, but rather which assumption is supported by the science, in particular whether the "genotoxic potential" of these hormones exhibits a threshold below which it will not be realized *in vivo*. He also does not cite any evidence that supports the EC's conclusion that no such threshold exists.

78. Dr. Guttenplan appears to be more explicit in his suggestion that the science relied upon by the EC supports its conclusion, but his answer is at the same time contradictory. In admitting that "repair enzymes are unlikely to be saturated" at physiological levels, he seems to suggest that there is a level at which repair will always occur. He then goes on to say that "[f]or any toxin the dose determines the risk". These two statements together suggest that at the dose to which consumers are exposed to oestradiol 17 β residues from treated meat, the "genotoxic potential" of these hormones is not relevant. This is consistent with what the other experts have indicated: that there is indeed a threshold below which these hormones are safe.

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?

79. Drs. Boisseau, Boobis and Guttenplan all consider the EC's conclusions about the absence of thresholds to be inconsistent with the Codex standards, whereas it remains somewhat unclear what Dr. Cogliano thinks about this issue. However, to the extent that most of the experts found that the EC's conclusions on the matter are unsupported by the evidence and are "questionable", they support the existing Codex standards.

80. Dr. Boobis elaborates on the concept of "incremental risk"; first by clarifying what in his mind is the more important issue of whether low levels of exposure affect "circulating levels". He makes three important points: (1) homeostatic control mechanism combined with low bioavailability means there is a "range of exposures for which there are compensatory alterations in endogenous levels"; (2) depending on endogenous levels, which vary by physiological state, some increments in exposure may "perturb endocrine effects", but these exposures would have to be above the ADI; and (3) genotoxic effects, to the extent that they will occur at all, will respond more to the natural variations in endogenous levels than the small changes in these levels that might arise from hormones from meat from treated animals. All of these points support the conclusion that there are clear thresholds for exposure to exogenous sources of substances that are also produced endogenously in variable amounts.

81. The experts' answers also confirm again that even though JECFA acknowledged that oestradiol 17 β has "genotoxic potential", this acknowledgement did not generate concern about the safety of the substances and therefore did not affect its recommendation. JECFA essentially did not consider that this "genotoxic potential" was relevant to the carcinogenic effects of oestradiol 17 β , which it considered dependent on hormonal activity.

82. For his part, Dr. Guttenplan attempts to justify the EC's conclusion with reference to new "areas of concern, such as developmental effects". However, Canada has some difficulty understanding the relationship Dr. Guttenplan seems to be drawing between the purported inability to

set thresholds for genotoxic substances and the identification of new concerns that appear to result from hormonal activity. Dr. Guttenplan seems to be using new concerns about one type of adverse effect (developmental effects) to demonstrate that concerns about the occurrence of another type of adverse effect (genotoxicity) are justified. The Panel may wish to ask Dr. Guttenplan to elaborate on the relationship he suggests in this response.

Q21. Does the scientific evidence referred to by the European Communities demonstrate that the five hormones other than oestradiol 17 β , 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]

83. Drs. Boisseau, Boobis and Guttenplan all refute the EC's claims about the potential genotoxicity of the other five hormones. Drs. Boisseau and Boobis survey the various tests by which these substances failed to show genotoxicity (the former in his answer to Question 16), and Dr. Guttenplan simply states generally that there is "no conclusive evidence presented by the EC" that they have genotoxic potential.

84. Whereas Drs. Boisseau and Boobis both indicate without qualification that the failure to follow GVP would not affect the "genotoxic potential" of the five hormones, Dr. Guttenplan's advice on this matter contradicts his advice given in response to other questions. In some of his other responses, he seems to support the EC's contention that no threshold can be established for substances that are genotoxic. At the same time, he provides in his response to this question that genotoxic effects will be "minimized by good veterinary practice". To the extent that the purported risks from failure to follow GVP are that cattle (and ultimately consumers) will be exposed to higher doses, Dr. Guttenplan seems to be suggesting a dose-response relationship between exposure to hormones and genotoxicity. The Panel could ask him to clarify his views on whether there is a dose-response relationship.

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]

85. Drs. Boobis and Guttenplan both extensively discuss the effectiveness of DNA repair mechanisms in what the former calls a "flexible and very efficient DNA repair process" and what the latter considers a mechanism with "considerable redundancy". They also both agree that the repair mechanisms that operate to repair the "considerable oxidative DNA damage" (Dr. Boobis) caused by endogenous processes are as effective for damage caused by exogenous agents.

86. Importantly, Dr. Boobis points out that because of DNA repair mechanisms, the creation of DNA adducts does not in itself always indicate that mutations will occur, let alone malignant neoplasms (*i.e.*, cancer). He further confirms that the kind of DNA damage that might be expected from hormones from meat from treated animals (*i.e.*, active oxygen) is also the kind of repair mechanism that is "amongst the most efficient".

87. For his part, Dr. Guttenplan makes some unsupported statements, in particular when he suggests that repair mechanisms are "not really relevant" to a risk assessment of oestradiol 17 β because the repair will not be different than for other types of damage. He does not attempt to describe the "other types of damage" and whether repair of these other types of damage means that such damage does not lead to adverse effects. In the absence of a specific assessment of the effectiveness of the repair mechanisms for comparable types of damage, the statement that they are comparable is not helpful.

88. Quite apart from the lack of clarity in Dr. Guttenplan's response, it is inconsistent with the more thorough advice provided by Dr. Boobis. The central issue differentiating JECFA's conclusion that even though oestradiol 17 β has "genotoxic potential" it is possible to establish an ADI, on the one hand, and the SCVPH's conclusion that oestradiol 17 β is genotoxic and therefore no threshold exposure can be determined, on the other, is the degree to which damaged DNA, if indeed it is damaged, is repaired and adverse effects avoided. Far from being "not really relevant", therefore, this issue is one of the most relevant issues to the resolution of the controversies surrounding the safety of these hormones. It is therefore also central to the issue of whether the EC has conducted a valid risk assessment.

89. With respect to whether the EC had failed to take into account these repair mechanisms in its evaluation, Dr. Guttenplan considers that it failed to do so. Ultimately, to the extent that the SCVPH takes so many short-cuts in its opinions on the basis that the hormones are seen to be genotoxic, the failure to address the role of mechanisms that counter this genotoxic potential is a critical shortcoming. Ignoring such evidence results in a significant overestimation of the risk, to the point of concluding there are risks where none exist.

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)]

90. There is both agreement and disagreement between the experts who answered this question (Drs. Boisseau, Boobis, Cogliano and Guttenplan) on the importance of cancer's long latency periods to the conduct of risk assessments that purport to identify cancer risks from hormones in meat. On the one hand, the experts tend to agree that the hormones in question have been in use long enough as growth promoters (a minimum of 20 years, according to some) for any long-term health effects to manifest themselves. On the other hand, they disagree about whether it is possible to positively identify the use of these hormones for growth-promotion purposes as the source of any observed adverse health effects. Dr. Cogliano does not weigh in on either of these points, confining himself instead to the observation that it is "definitely necessary" to take long latency periods into account in general, a point not disputed by any other expert.

91. Dr. Guttenplan advises that it is possible to identify a relationship between hormones consumed in meat and carcinogenic effects, but he does not explain how this would be accomplished. He provides no information on how to account for the fact that the populations he says would be studied to observe the relationship would also be exposed to many other sources of hormones other than that consumed through meat from treated animals, such that it would be very difficult to identify any causal relationship between the effect and the specific source.

92. Dr. Boobis is sceptical, but does seem to suggest that it might be possible with a well designed study involving "extremely large populations to detect any increase in cancer incidence". Dr. Boisseau is even more sceptical that a relationship can be identified with any certainty, finding not

only that it is not possible to study such a relationship, but it is not even "useful". Drs. Boisseau and Boobis explain their scepticism in two separate, but related, ways: the former says it would be impossible to discriminate between different factors in allocating responsibility (see also the experts' responses to the next question on confounding factors); the latter says that since the risk from such a small dose is so minimal, "it is questionable whether an increase in risk, even if it existed, could be detected in exposed populations." In other words, epidemiological studies are of little use in risk assessments of hormones in meat from treated cattle.

93. The answers from these two experts confirm again the essential point: 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. Given the wide variety of sources of, and variability of exposure to, hormones, any correlation observed between exposure to hormones and adverse effects cannot be attributed to the single source of hormones that comes from residues of hormones in meat from treated animals. Nothing in the SCVPH's opinions, in the scientific evidence submitted by the EC, or in the answers of the experts supports a conclusion other than this.

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?

94. Drs. Boisseau, Boobis, Cogliano and Guttenplan all agree that it is extremely difficult to attribute causal roles to different confounding factors in the study of the causes of cancer, even as some of them advise that it is at least possible to identify what some of these factors may be. According to Dr. Boobis, this would be particularly the case in the circumstances of these hormones, where "the risk from the confounder is appreciably greater than the risk of the exposure of interest".

95. To the extent that any of the experts respond to the second part of the question, they seem to suggest that the difficulty with attributing causality to a specific factor reduces the value of epidemiological studies in risk assessments of the nature under review here (*i.e.*, where the source of the agent under review comprises such a small amount of overall exposure and the adverse effects have multiple causes). Dr. Boobis offers the view that confounding factors do not affect the risk assessment, but the "interpretation of the data used in the risk assessment", which Canada understands to mean that all causal factors should be taken into account, and not just single factors.

96. Contrary to advice from the experts that it is extremely difficult to isolate confounding factors in circumstances such as these, the EC has claimed that it has done just that. It has taken observed adverse effects and then has ascribed the cause of these effects to one source of hormones (that from meat from treated animals). In light of the advice from the experts, the EC has failed on two accounts: it has not observed adverse effects that can be co-related to hormones; and even to the extent that it has observed such effects, it has not investigated the role of hormones writ large, preferring instead to focus on the single source of hormones.

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]

97. Drs. Boisseau, Boobis and Guttenplan expressly deny that the three studies referred to by the EC confirm a risk to human health from exposure to hormone residues from meat from treated animals. Only Dr. Cogliano endorses the EC's attempt to use these studies as evidence of risk from consuming hormones from meat from treated animals, but he does so without any supporting evidence or analysis.

98. With respect to the study on zeranol⁴⁶, Drs. Boobis and Guttenplan both indicate that the study was based only on *in vitro* experiments and therefore cannot be extrapolated to human exposure. They find it particularly difficult to extrapolate to exposure from meat consumption since the dose used in the study was high, a point that even Dr. Cogliano acknowledges. In response to the observations of positive genotoxicity findings *in vitro*, Dr. Boobis notes that "genotoxicity by this mechanism [redox cycling] should exhibit a threshold and is also militated against *in vivo* by antioxidant defence systems and efficient repair of oxidant-damaged DNA."

99. With respect to the study on the relationship between intake of red meat and colorectal cancer,⁴⁷ Dr. Boisseau simply refers to his general scepticism of the ability of epidemiological studies to identify specific causal agents due to confounding factors. Dr. Boobis is even more specific in dismissing the relevance of this study, noting that its results are not new, that they are consistent across geographical area, and that even the authors point to possible explanations, such as the formation of mutagens during the cooking of meat and the generation of nitroso compounds. He notes that the study provides "little support for a contribution from hormones present in meat from their use as growth promoters ... because the association is just as strong in regions where hormones are not used as where they are used".

100. Dr. Boobis is the only expert to make any detailed comments on the study of the relationship between hormone replacement therapy and the incidence of breast cancer.⁴⁸ He notes again that this study did not find any relationship that had not already been observed in the past, and that had not already been acknowledged by JECFA. The real issue, therefore, is not whether there is such a relationship, but whether that relationship has any relevance for the assessment of risk from the consumption of hormones in meat from treated animals. On this point, Dr. Boobis advises that it does not, because the "weight of evidence is such that the hormones cause cancer by a mechanism exhibiting a threshold" and the doses of hormones involved in this study were considerably higher than that found in meat from treated animals.

101. Ultimately, the experts' reactions to the specific quote from the EC (about the studies having been conducted after the ban) capture the overall response to the EC's use of these studies. Dr. Boisseau considers that this comment "expresses a concern but does not provide any scientific evidence supporting this concern", whereas Dr. Guttenplan considers that it "negates any relevance to the possible connection of hormone-treated meat consumption and cancer". Dr. Boobis considers that the only way the timing of the studies would matter would be if it were proven that there were risks from hormones from meat from treated animals, which Dr. Boobis confirms again has not been demonstrated. Dr. Boobis is more pointed in his criticism of the EC's suggestion that "it can not be excluded" that there is greater risk. He advises that since the same statement can be made in the absence of any study whatsoever of the risk from hormones, this statement is "not scientifically defensible".

⁴⁶ Exhibit EC-73.

⁴⁷ Exhibit EC-71.

⁴⁸ Exhibit EC-72.

102. These reactions highlight a tactic employed by the EC, namely, the manipulation of a genuine scientific interest in assessing the possible adverse effects arising from exposure to a substance in general (*i.e.*, hormones) to create specific and unjustified concern about possible adverse effects from one single and insignificant source of that substance in particular.

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]

103. As with their responses to the previous questions related to the potential of epidemiological studies, Drs. Boisseau, Boobis, Cogliano and Guttenplan all agree that the studies relied upon by the EC, in particular the epidemiological studies, do not identify a relationship between cancer and residues of hormones from meat from treated animals.

104. Many of the reasons they provide have already been discussed above, such as confounding factors, *etc.* The EC places considerable emphasis on statistics comparing breast and prostate cancer rates between Europe, where hormones are banned for growth-promotion purposes, and North America, where they are not. Not surprisingly, while there may be some observable differences in rates between certain regions and ethnic groups, on the whole the rates are relatively similar. The experts agree that the differences that do exist are so slight as to be not statistically significant. To the extent that there are differences at all, Dr. Boobis cautions against inferring too much from geographical differences in cancer rates, because of what he calls an "ecological fallacy" (the belief that differences observed between groups will also be observed between individuals). More importantly, none of these studies relied upon by the EC included assessments of data on hormone intake, so even if the differences were significant (and they are not) no link can be made between these statistics and the consumption of meat from animals treated with the hormones at issue.

(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?

105. The experts who respond to this question (Drs. Boisseau and de Brabander) agree that since the chemical structures of the three synthetic hormones (zeranol, trenbolone acetate (TBA) and melengestrol acetate (MGA)) are different from the structure of the three natural hormones (oestradiol 17 β , testosterone, progesterone), the residues of the synthetic hormones in the meat of treated cattle will be different from the residues in meat from cattle treated with natural hormones.

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?

106. Dr. Boisseau and Dr. de Brabander address this question. Dr. Boisseau states:

The definition of residues encompasses both the parent substance and all the metabolites derived from this parent substance. Therefore, in the case of the part of residues of the natural hormones which consists of parent substances, there is no difference between hormones naturally present in food producing animals, meat or

human beings. Metabolites of these natural hormones existing in cattle and meat are, obviously, the same. To my knowledge, there is no scientific evidence showing that the main metabolites of the three natural hormones existing in cattle and humans are not similar.

107. For the sake of clarity, the Panel may wish to ask that Dr. Boisseau clarify whether the residues, both parent and metabolite, in meat from cattle treated with the three natural growth promoting hormones are the same as their respective endogenous natural hormones found in animals, meat or human beings.

108. Dr. de Brabander's opinion is much less clear. First he states that "there are no differences", then he qualifies his statement with references to unspecified "ongoing research". He states that "[t]he residues of the natural hormones in cattle are in the 17 α form (inactive) while the use of 'natural' hormones used for growth promotion purposes may lead to residues in the β form (active form)." If Dr. de Brabander is suggesting that residues of natural hormones in untreated cattle do not occur in the β (active) form, he is contradicting his own answer to Question 31. There, he agrees that "residue levels in meat from hormone-treated cattle are well within the physiological range of residue levels in untreated cattle". Moreover, 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.⁴⁹

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]

109. Dr. Boisseau confirms that the level of residues is typically taken into consideration at the third step of the risk assessment process, namely the exposure assessment, after the ADI has been established. The purpose of evaluating the level of residues in food is to ensure that dietary exposure to the substance does not exceed the ADI. Dr. Boisseau confirms that the SCVPH did not "conduct a quantitative assessment of the exposure of consumers to the residues of [synthetic] hormonal growth promoters including the determination of the levels of residues in food from treated animals, the impact of the non observance of good veterinary practices on these levels and the comparison between these levels and the MRLs set up by Codex".

110. Dr. de Brabander fails to directly answer the Panel's question. Instead, he appears to offer his own opinion regarding the inaccuracy of published concentrations of residues. Referring to Table 8 in the SCVPH 1999 Opinion⁵⁰, he indicates that residue levels for trenbolone are "extremely low...and serious doubts about their accuracy can be made." Table 8 is drawn in part from the extensive review of residue data contained in the JECFA Monograph to the 34th Meeting.⁵¹ By quoting the JECFA data without qualification, the SCVPH does not appear to share Dr. de Brabander's concerns about the

⁴⁹ JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12 (Rome: FAO, 2000), at p. 38 (Exhibit CDA-17).

⁵⁰ 1999 SCVPH Opinion, Section 4.4.2, at p. 56 (Exhibit CDA-2).

⁵¹ JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Thirty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food and Nutrition Paper, No. 41/2 (Rome: FAO, 1990), at pp. 88-100, in particular p. 96 (Exhibit CDA-38).

inaccuracy of the trenbolone residue data.⁵² In any event, in contrast to the JECFA analysis, Dr. de Brabander fails to provide a single reference for his conclusion that "concentrations may seriously be underestimated."

111. Dr. de Brabander's statement that the MRLs set by Codex are high in relation to "modern analytical limits" is confusing. MRLs are a function of the ADI and are not set on the basis of detection methods, but toxicological data. As Dr. Boisseau states in response to Question 32, for control purposes, a validated analytical method need be only as sensitive as is necessary to detect residues at the established MRL. Thus, it makes little sense to assert that the MRLs are high unless there is evidence to suggest that the ADI is set too high. Moreover, Dr. de Brabander lists the MRL for MGA, an MRL that was recommended by JECFA as recently as February 2004 (62nd meeting). Dr. de Brabander appears to suggest that the analytical techniques used by JECFA in 2004 were not sufficiently "modern". However, his cursory conclusion is in stark contrast to the extensive evaluation of residue data conducted by JECFA.⁵³ 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.⁵⁴ All ten studies cited date from 1999 to 2002.

112. Lastly, Dr. de Brabander indicates that "[a]s demonstrated in several documents a major part of the hormones used are excreted through the faeces (for MGA ca. 75%)..." It would be helpful if Dr. de Brabander could provide citations for documents to which he refers. In addition, for completeness, it would be helpful if Dr. de Brabander could provide corresponding statistics in relation to excretion for all the hormones at issue, synthetic and natural.

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]

113. Both Dr. Boobis and Dr. Boisseau confirm that the SCVPH did not itself evaluate evidence of actual residue levels of the three natural hormones in its assessment of risks from such residues.⁵⁵ In addressing the impact of GVP on residue levels in meat, Dr. Boobis explains that, while the SCVPH considered potential exposure following inappropriate use scenarios, "these data are limited in the

⁵² 1999 SCVPH Opinion, Section 4.4.2, at p. 56 (Exhibit CDA-2).

⁵³ See JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Sixty-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/16 (Rome: FAO, 2004) (Exhibit CDA-33); JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/14 (Rome: FAO, 2002) (Exhibit CDA-35); and JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/13 (Rome: FAO, 2000) (Exhibit CDA-37).

⁵⁴ JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/14 (Rome: FAO, 2002) (Exhibit CDA-35), pp. 56-59. All of the 10 studies cited by JECFA in this Monograph are from 1999-2002.

⁵⁵ Dr. Boobis, at p. 33. Dr. Boisseau refers back to his answer to Question 29, in which he concluded that the EC failed to "conduct a quantitative assessment of the exposure of consumers to the residues of [natural] hormonal growth promoters including the determination of the levels of residues in food from treated animals, the impact of the non observance of good veterinary practices on these levels and the comparison between these levels and the [ADI] set up by Codex."

absence of any information on the frequency of occurrence of such misuse in the use of the products in question." Moreover, he confirmed that "[i]t would have been possible to compare the SCVPHs estimates of exposure [in the misuse scenarios] with the ADIs derived by the JECFA but this was not done." Lastly, he concludes that the "ADI would have exceeded the exposure estimates for the three [natural] hormones." This advice supports the conclusion that the EC has not properly assessed the potential occurrence of adverse affects from the misuse of the natural hormones in question.

114. Unfortunately, Dr. de Brabander fails to directly answer the Panel's question. Instead, he refers to "old" data for residue concentrations and concludes without any analysis that their "accuracy could be doubted." Rather than responding directly to the Panel's question, he discusses, amongst other things, the potential environmental effects of hormone residue in excrement and the side-effects of testosterone spray used to enhance a woman's enjoyment of sex.

Q31. Please comment on the US statement that "concentrations of oestradiol 17 β 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 17 β in treated cattle may be slightly higher than those in untreated cattle, this increase is much smaller than the large variations observed in (reproductively) cycling and pregnant cattle and is thus well within the range of naturally observed levels." 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]

115. Dr. de Brabander offers qualified agreement with the US statement.

116. Both Drs. Boisseau and de Brabander indicate that meat consumption from pregnant heifers is exceptional. However, this conclusion is at odds with the evidence considered by the UK Sub-Group of the Veterinary Products Committee.⁵⁶ The Sub-Group analyzed the effect on exposure to oestradiol 17 β in meat from the termination of the Over Thirty Months Scheme (OTMS) in the UK, a program that removes culled adult cows from the food chain. The Sub-Group concluded that "the removal of these pregnant cull cows to the food chain [as a result of the OTMS] has reduced the quantity of oestradiol in the food chain by 37% ... which will be returned as the BSE controls are removed and the market returns to normal."⁵⁷ This is based on the assumption that 25% of slaughtered cows are in calf, at stages of pregnancy evenly distributed over the three trimesters.

117. In a different vein, Dr. Boisseau's response to this question also supports Canada's basic point that the EC is attempting to divorce the use of growth-promoting hormones from their appropriate context and, as a result, presents a distorted assessment of the risks associated with the use of growth-promoting hormones. He states:

Even if, accepting the substance of the EC comment [meat consumption from pregnant heifers is exceptional], it is possible to limit the physiological range of

⁵⁶ UK, Sub-Group of the Veterinary Products Committee, *Executive summary and critical evaluation of the scientific reasoning and methods of argument adopted in the opinion of the Scientific Committee on Veterinary Measures Relating to Public Health which assessed the potential risks to human health from hormone residues in bovine meat and meat products*, October 1999 (Exhibits CDA-6, US-12).

⁵⁷ *Ibid.*, at para. 56, pp. 19-20.

oestradiol 17 β and of progesterone in cattle, it has nevertheless to be recognized that (1) consumers are exposed to these two natural hormones through their consumption of meat and milk from the different non treated food producing animals and, mainly as least for women, through their endogenous production, (2) this exposure cannot be avoided. Therefore, the use of the concept of threshold in the risk assessment of the natural hormone residues is legitimate and the additional intake of residues of these natural hormones from the meat from treated cattle has to be considered in this context and not according to a theoretical "no additional intake of residues is acceptable".[emphasis added]

118. In essence, Dr. Boisseau advises 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. To posit that the risks arising from the use of HGP's are such that no threshold for acceptable intake can be established is simply irrational and scientifically unjustified.

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?

119. The SCVPH's statement concerning ultra-sensitive detection methods appears to relate its discussion of analytical techniques set out in Section 4.1.1 of its 2002 Opinion. In that section, the SCVPH acknowledges that the "low number of samples does not allow a qualified validation of typical characteristics such as sensitivity, specificity, accuracy and reproducibility (study 1, study 8)."⁵⁸ The experts who answered this question appear to agree on the importance of validating analytical methods.⁵⁹ Dr. Boisseau states that "validation must be carried out in compliance with well defined and internationally accepted criteria". These criteria include accuracy, precision, sensitivity, specificity, reproducibility, and reliability.⁶⁰

120. In terms of the second part of the Panel's question, Dr. Boisseau explains that once an MRL has been established, the sensitivity of the validated analytical method need only be consistent with the values established by the MRLs. Analytical methods that are more sensitive, or "ultra sensitive," are redundant for control purposes.

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)]

⁵⁸ EC, Health & Consumer Protection Directorate-General, *Opinion of the Scientific Committee on Veterinary Measures Relating to Public Health on Review of previous SCVPH opinions of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products*, adopted April 10, 2002, Section 4.1.1, at p. 9 (Exhibit CDA-7). See also p. 21.

⁵⁹ Drs. Boisseau and de Brabander.

⁶⁰ JECFA, *Procedures for Recommending Maximum Residue Limits*, at p. 37 (Exhibit CDA-44).

121. Three experts respond to this question. JECFA also responds to the same question asked of the international bodies (Question 20). JECFA indicates that it can decide to re-evaluate previous assessments when it is made aware that there are new data which may be pertinent to the risk assessment of the substances in question. The claim by the EC in *EC – Hormones* that it had new evidence showing that oestradiol 17 β was a direct acting genotoxic carcinogen appears to have promoted, at least in part, JECFA's 1999 re-evaluation. Moreover, JECFA indicates that new studies had also been published for the other hormones. This is consistent with the advice of Dr. Boisseau.

122. In terms of whether the residue data for the natural hormones used in 1999 were the same as those used in 1988, JECFA indicates that while most of the residue studies were the same, a few additional studies were reviewed. JECFA also states that it performed a more detailed review of the validity of the analytical methods used in the studies and used only data generated using valid methods.

123. JECFA also confirms that in the 1999 evaluation new toxicological and epidemiological data for the three natural hormones were evaluated, a position that is supported by Dr. Boobis. JECFA is quite specific as to the new information that was not available to it in 1988 but was available and considered by it in 1999.

124. In terms of whether the conclusions from the two evaluations differed, Dr. Boisseau confirms that in substance the conclusions remained the same. The risk assessment indicated a wide margin of safety for consumption of residues in meat from treated cattle. Hence, the establishment of numerical MRLs was not necessary to protect human health.⁶¹

125. As to the reasons for establishing ADIs for the three natural hormones in 1999, JECFA refers to "[t]he additional data reviewed and the need to establish and [*sic*] ADI as quantitative estimate for a safe oral intake".⁶² This is consistent with Dr. Boobis' explanation that in the intervening years between the first and second JECFA evaluations, it became clear that exposure to natural hormones, albeit at levels much higher than that found in meat from treated cattle, could have adverse effects in humans. The implicit conclusion was that it was necessary to establish ADIs as benchmarks to ensure that exposure to these hormones through dietary sources did not cause adverse effects observed in other areas.

126. JECFA confirms that "the establishment of an ADI implies that there is a threshold of effect for such a compound, below which now [*sic*; read "no"] toxicological effects occur".⁶³ This conclusion is supported by both Dr. Boisseau and Dr. Boobis.

127. As to the reasons for CCRVDF's not having considered JECFA's more recent recommendations in respect of the natural hormones, JECFA's answer to Question 20 (to the international bodies) includes a direct quote from the 12th CCRVDF report, which states:

Recognizing that this Committee had not requested the re-evaluation of these substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, the Committee decided not to consider these new recommendations.

128. As Dr. Boobis explains, the result is that Codex continues to list the three natural hormones with an indication that MRLs are "unnecessary" for tissues from cattle.

⁶¹ JECFA's answer to Question 20 (to the international bodies), at p. 18.

⁶² *Ibid.*

⁶³ *Ibid.*

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)]

Outdated Residues Data

129. Dr. Boisseau confirms what is generally accepted within the scientific community: that scientific data do not deteriorate simply because of the passage of time. He concludes that "the quality and the number of the available data are more important than the dates at which these data have been produced." Dr. Boisseau also confirms that it is standard practice for JECFA to determine the quality and sufficiency of the data under consideration in its assessment of substances, as well as the validity of the analytical methods employed.⁶⁴

130. In the specific case of the hormones at issue, Dr. Boisseau confirms that:

JECFA has considered that the quality and the number of the available residue data were satisfactory and therefore the fact that these data were not new had no specific impact on its evaluation.

131. Thus, the EC's suggestion that old data are necessarily unreliable data is simply groundless. Obviously old data that have been generated using validated analytical methods are to be preferred over more recent data generated by unvalidated and widely ignored analytical techniques. At the end of the day, the expert advice supports Canada's position that sufficient scientific evidence exists to conduct a risk assessment for all six of the hormones at issue.

Type of Data and Extrapolations from Animal to Human

132. It should first be noted that the EC's statement in paragraph 102 of its Rebuttal Submission makes little sense. Studies with experimental animals are always *in vivo* and cannot by definition be *in vitro*. *In vitro* studies are studies that are conducted in an artificial environment outside the living organism.

133. To the extent that the EC's statement suggests that there is something unusual or inappropriate about making extensive use of studies with experimental animals and general studies by IARC, the experts' responses to this question demonstrate that such a suggestion is nonsense. Understandably, Dr. Boisseau expresses surprise with the EC's statements, stating:

... it is the normal way for assessing the toxicological potential of a substance to take into consideration *in vivo* studies with experimental animals, *in vitro* studies and also reports already published by internationally recognized scientific organisations such as IARC.

134. Where human studies are not available, which is typically the case, for ethical reasons, risk assessors resort to these other studies out of necessity. Extrapolations from animal studies to humans

⁶⁴ For a description of JECFA's approach to data quality, see EHC-70, at pp. 22-23. ("JECFA has always judged studies on their merits, the main criteria being that the study was: (a) carried out with scientific rigour, and (b) reported in sufficient detail to enable comprehensive evaluation of the validity of the results.")

have been standard practice for many years and regularly applied by international and national agencies in the conduct of risk assessments for food additives and contaminants, as well as veterinary drugs. It should be emphasized however, that in the case of the natural hormones, JECFA made extensive use of data derived from human studies involving the three natural hormones, in addition to animal studies. Moreover, this statement is all the more surprising when one considers that the very type of studies that the EC appears to suggest are inappropriate are precisely the type of studies relied upon by the SCVPH.

135. As the experts confirm, the data and process used for assessing the safety of the hormones at issue are the same as those used for other veterinary drugs. JECFA has applied well-recognized procedures and principles in conducting its various risk assessments for the hormones at issue. Rather, the EC has strayed from internationally recognized techniques and methodologies.

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]

136. Dr. Boisseau's answer to Question 34 also applies to this question, namely, that the quality and quantity of data are more important than the date upon which the data were generated.

137. While the studies referred to in the 2000 JECFA Report on MGA date back to the 1960s and 1970s⁶⁵, JECFA assessed these data to determine whether the quality and quantity were sufficient to conduct its risk assessment. As Dr. Boisseau concludes, "JECFA considered a wide series of toxicological studies in its assessment, used as end point a non hormonal effect dose by far more conservative than a NOAEL based on tumorigenic effect and adopted a 200 safety factor to derive an ADI from this NOAEL."

(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]

138. Two of the three experts who responded to this question (Drs. Boobis and Boisseau) confirm that a dose-response assessment is a necessary component of hazard characterization. While these experts also acknowledge that such an assessment may not be feasible or required for substances that are genotoxic *in vivo*, they both confirm that this exception is not absolute. Dr. Boisseau confirms that this exception only applies to xenobiotic substances (*i.e.*, those that are foreign to the human body) or to substances with "genotoxic potential" where it is thought that this potential can be expressed in *in vivo* conditions. At least for the natural hormones involved here, neither of these conditions is met such that a dose-response assessment should be skipped.

⁶⁵ Exhibit CDA-37.

139. Dr. Boobis similarly describes at least two general sets of circumstances in which a dose-response assessment would still be conducted on substances thought to have genotoxic potential. First, if the mechanism of action of the genotoxic effect was known, and it was of the type of mechanism that is known to exhibit a threshold (for example, substances with kinetic or dynamic causes, as well as those caused by reactive oxygen species), then a dose-response assessment is necessary. Second, if the mechanism of action of genotoxicity was known or assumed to be DNA-reactive, then this genotoxicity would need to be confirmed *in vivo* before it would be appropriate to dispense with a dose-response assessment. As we know from numerous sources, including the EC risk assessment itself, it has not been demonstrated that any of these six hormones have genotoxic potential *in vivo*. According to the experts, this requires that a dose-response assessment be conducted.

140. Dr. Cogliano's short response suggesting a dose-response may not be required tells only half the story. His comments seem to be limited to circumstances involving a "hazard-based approach", without explanation of when such an approach is or is not appropriate. A hazard-based approach simply identifies whether a substance is *capable* of causing an adverse effect under certain conditions, and not whether such adverse effect would actually occur at given doses. This corresponds only to the "hazard identification" stage of a risk assessment (*i.e.*, whether a substance can cause an adverse effect) and disregards the hazard characterization stage, which includes an assessment of the dose required to provoke the identified hazard (*i.e.*, dose-response assessment).⁶⁶ Quite apart from the explanation from Dr. Boobis that a "hazard-based approach" is not appropriate for these hormones, it would also be inconsistent with obligations under the *SPS Agreement* that a substance be evaluated for the potential for occurrence of an adverse effect.

141. Dr. Cogliano's view that a dose-response assessment is optional is inconsistent with his later view that it is "widely accepted that adverse effects arising from hormonal activities depend on the dose".

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]

142. Drs. Boisseau and Boobis confirm Canada's statement that international techniques require that a dose-response assessment always be conducted as part of an assessment of the risk from chemical substances such as the six hormones. Dr. Boisseau indicates that it would not be possible to establish an ADI, and Dr. Boobis indicates that it would not be possible to recommend MRLs, in the absence of a dose-response assessment. These opinions are confirmed by JECFA in its response to Question 8 to the international bodies. In light of the universally held view that the adverse effects of hormones are dose-dependent, these answers are not at all surprising given the purpose of the dose-response assessment of determining as closely as possible the level of dose at which there is no response (*i.e.*, the NOAEL).

(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.

143. In presenting various figures for background levels of sex hormones of different age groups in response to this question, Dr. Boisseau raises concerns, as many others have done, about the reliance

⁶⁶ See Canada's comments on the experts' responses to Question 11.

by the EC on a new "ultrasensitive bioassay" (also referred to as the Klein assay). In light of the SCVPH's decision to revise downward by 100-fold the estimated physiological level of hormones in pre-pubertal boys and girls, and the significance of the conclusions it draws as a result, Dr. Boisseau raises the important point about whether this assay has been validated. More detailed discussion of the flaws of this methodology follow in Canada's comments on the experts' responses to Question 40.

Q39. Please comment on the SCVPH opinion stating that "any excess exposure towards oestradiol 17 β 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]

144. In his reply to this question, Dr. Boisseau confirms that the EC has failed to compare quantitatively the exposure to oestradiol 17 β from meat from treated animals to that from meat from non-treated animals and other sources of oestradiol 17 β . Without having conducted such a comparison, the SCVPH is unable to claim that such exposure is "excess", nor that, even if it is "excess", the amount of the excess would be sufficient to "present a potential risk to public health".

145. While Dr. Sippell offers the view that the EC's claim is supported, the evidence he refers to largely involves the controversial, and yet-to-be validated, methodology for measuring background levels of oestradiol 17 β (*i.e.*, the Klein assay). Quite apart from the fact that serious concerns have been expressed about the validity of this methodology,⁶⁷ the use of the methodology does not, on its own, support the conclusion that exposure to oestradiol 17 β residues from treated meat amounts to "excess exposure", nor that it "presents a potential risk to public health". Almost all the studies cited by Dr. Sippell apply to oestrogen in general, and not to residues of oestradiol 17 β consumed via meat from treated animals.

146. Therefore, when Dr. Sippell refers to "elevated estrogen levels", he provides no evidence whatsoever that such levels are achieved from the consumption of residues of hormones from meat from treated animals. On the contrary, to the extent that his greatest concern appears to be for exposure to oestradiol 17 β during "early life" (*i.e.*, pre- and post-natal periods), Dr. Sippell provides no evidence for, nor even a plausible explanation of, exposure at this age to residues from meat products. Certainly a foetus/infant could be exposed via the mother, but since late pregnancy and early *post partum* are the periods of a woman's life where the natural oestrogen level is at its most elevated, the proportion of oestrogen exposure of the foetus/infant that would come from the consumption by the mother of meat from treated animals would be trivial.

147. Moreover, a review of the full context of the quote cited in the question⁶⁸ reveals that it is based on conclusions that the experts have contested elsewhere in their replies. Citing disputed findings that metabolites of oestradiol 17 β have "genotoxic potential", the SCVPH concludes that oestradiol 17 β is both a tumour initiator as well tumour promoter. It then suggests that this conclusion is confirmed by epidemiological data and IARC's classification of oestrogen as a human carcinogen. On the basis of these findings, the SCVPH further concludes that "any excess exposure... presents a potential risk to public health".⁶⁹ However, in establishing the adverse effect threshold as "any excess exposure", the SCVPH offered no confirmed evidence of genotoxicity of the substances, nor any scientific support for its suggestion of a link between epidemiological data and its conclusions. The result is that the quote from the SCVPH's opinion is no more than speculation based on tenuous links drawn between unsupported conclusions.

⁶⁷ See Canada's comments on Question 40.

⁶⁸ 1999 SCVPH Opinion, at pp. 74-75 (Exhibit CDA-2).

⁶⁹ *Ibid.*, at p. 74.

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?

148. Drs. Boisseau and Boobis both share concerns about the methodology (an "ultrasensitive" recombinant cell bioassay (RCBA) developed by Klein and others⁷⁰) that generated the underpinning the conclusion that endogenous levels of hormones in pre-pubertal children are lower than previously thought. Dr. Boisseau's concerns about the absence of validation of this methodology are reflected in his answer to Question 38.

149. Dr. Boobis echoes these concerns in a very comprehensive review of the issues surrounding this controversial methodology. While he acknowledges that endogenous levels may be lower than previously thought, Dr. Boobis expresses grave doubts that this is by the "orders of magnitude" suggested by the SCVPH, repeating Dr. Boisseau's concern when he says that the "reliability of the Klein *et al.* assay has yet to be determined". He points to a number of contradictory results in the use of this assay, including from the original inventors themselves, that at the very least suggests that it has not been adequately validated for use in a risk assessment.

150. The concerns highlighted by the experts about the SCVPH's use of this methodology have been consistently cited by others as one of the flaws in the analysis of the SCVPH. For example, the UK Sub-Group Report early on expressed the concern that the Klein assays have not been appropriately validated. It expressed:

... concerns about the reliability of this analytical approach, which has been very little used in peer-reviewed publications other than by the originators of the assay, despite its initial publication in 1994. These concerns throw doubt upon the values derived by Klein *et al.* and therefore also on the conclusions of the [SCVPH] opinion.⁷¹

151. Not only does the SCVPH fail to point out the obvious problems with the validity of the Klein data, but it ends up comparing apples with oranges. The 1999 SCVPH Opinion recognizes that "perhaps the hormone residues in beef, which are also low and which have also been determined by Radio Immune Assays (RIA) are equally variable and over representative of the actual hormone concentrations."⁷² Thereafter, without acknowledging that it is using two different analytical techniques, the SCVPH goes on to compare concentrations of oestradiol in beef using RIA with concentrations in plasma using the Klein assay. As the UK Sub-Group Report concluded, "[t]his is inappropriate and may lead to a biased inappropriate perspective."⁷³

152. Most importantly, even the 1999 SCVPH Opinion calls the data produced by Klein *et al.* "experimental evidence", calling the data "insufficient" to form the basis of a sound risk assessment.⁷⁴ A few years later, the SCVPH itself concluded in its 2002 opinion that "[t]he obtained results suggest

⁷⁰ *Ibid.*, at pp. 30 and 38.

⁷¹ UK Sub-Group Report, at pp. 26-28 (Exhibit CDA-6).

⁷² 1999 SCVPH Opinion, at p. 30 (Exhibit CDA-2).

⁷³ UK Sub-Group Report, at para. 96, p. 28 (Exhibit CDA-6).

⁷⁴ 1999 SCVPH Opinion, at pp. 38-9 (Exhibit CDA-2).

that the use of recombinant yeast and rainbow trout hepatocytes to detect oestrogenic compounds is not justified in view of their lack of sensitivity."⁷⁵).

153. Contrary to the concerns expressed by at least two of his colleagues, Dr. Sippell seems to believe the recombinant yeast bioassay (RCBA) methodology constitutes a "quantum leap" in assay methodology. In support of this claim, Dr. Sippell cites a later study (Paris *et al.*, 2002) to suggest that the Klein RCBA has been validated. Interestingly, the research by Paris *et al.* was also cited by Dr. Boobis in support of his opinion that the Klein RCBA had not been validated by subsequent research because the research by Paris *et al.*, which in Dr. Boobis' mind is more credible, demonstrated that the Klein RCBA overestimated background oestrogen levels by up to 18 times. The Paris *et al.* results in fact were closer to the original data used by JECFA based on the RIA methodology. In light of these discrepancies, the Panel may wish to ask Dr. Sippell to clarify why he believes the Paris *et al.* results validate the 1994 Klein results.

154. Dr. Sippell makes another ambiguous observation in his advice when he states that "the complexity of the [Klein] RCBA so far prevents its wider use for routine measurements in small serum samples from infants and prepubertal children". Canada understands this to be confirmation that there are very little reliable data related to the use of RCBA.

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?

155. Drs. Boisseau and Boobis agree that although individuals with the lowest endogenous hormone levels are at the greatest risk from any adverse effects that might result from exposure to hormones, the exposure to hormones via meat from treated animals would not result in any change in the effect that would be expected from hormones from meat from non-treated animals, or any other exogenous source for that matter.

156. Dr. Sippell suggests that the risks would be different, but he bases his assessment of "risk" on what he calls a "new threshold", which appears to be based on the results from the Klein assay. However, as the experts have advised in response to previous questions, this assay has not been validated sufficiently to support the kinds of conclusions that Dr. Sippell makes.

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 17 β ? 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 17 β ?

157. Drs. Boisseau and Boobis both acknowledge the many ways in which JECFA takes into account the situation of sensitive populations. They point in particular to the use by JECFA in establishing the ADI for oestradiol 17 β of an additional safety factor of 10 specifically for sensitive populations, in addition to the initial safety factor of 10 for variation between individuals. The resulting safety factor of 100 makes for a very conservative assessment of safe exposure. Dr. Boisseau confirms that the safety factors for some of the other hormones were even greater. Moreover, Dr. Boisseau highlights two additional safety factors: first, that the estimated exposure to the natural hormones from meat from treated animals amounts to a very small proportion of the overall exposure from all sources, and, second, the fact that the bioavailability of the natural hormones is quite low.

⁷⁵ 2002 SCVPH Opinion, at p. 9 (Exhibit CDA-7).

The approach of JECFA builds in significant safety margins to take into account the situation of sensitive populations.

158. Only Dr. Sippell expresses concern about whether JECFA's analysis adequately takes into account the situation of sensitive populations, but his concern is based on estimates of endogenous levels in these populations that have been generated by the Klein RCBA. As discussed above, however, this methodology has not been adequately validated, and the original results obtained by Klein have not been reproduced by others. In light of more credible measurements of endogenous levels of hormones, Dr. Boobis indicates in his answer to Question 40 that exposure up to the ADI established by JECFA would still be safe for sensitive populations. Nothing in Dr. Sippell's comments (other than a non-validated methodology) contradicts the analysis conducted by Dr. Boobis.

159. Both Drs. Boisseau and Boobis indicate that the scientific material referred to by the EC does not require a revision of the Codex recommendation with respect to oestradiol 17 β .

(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), 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]

160. The experts generally agree that bioavailability refers to the fraction of the substance that is available for systemic circulation. It is normally estimated by comparing the availability of a substance after oral administration with the availability of a substance after intravenous administration (which is assumed to be 100% bioavailable). The experts also agree that only the bioavailable portion of the substance at issue can produce an adverse effect. As a consequence, only that portion of the substance that is bioavailable will be significant for risk assessment purposes.

161. Dr. Boisseau and Dr. Boobis confirm that the natural hormones are either inactive orally or have low bioavailability (between 5% to 10%). These conclusions are supported by both JECFA⁷⁶ and CVMP.⁷⁷ The JECFA analysis is based on a review of the scientific literature on the absorption, distribution and excretion of oestradiol 17 β set out in the Toxicological Monograph for the natural hormones prepared for JECFA's 52nd meeting.⁷⁸

162. Dr. Guttenplan indicates that the "bioavailability of estrogen is low but not insignificant (probably between 5 and 20%, if estrone is also taken into account[])." He further indicates that the SCVPH in its 1999 and 2002 opinions questions the sufficiency and accuracy of the data relied upon

⁷⁶ See JECFA, 52nd Report, at p. 58. (Exhibit CDA-16). ("In general, oestradiol-17 β is inactive when given orally because it is inactivated in the gastrointestinal tract and liver".)

⁷⁷ European Medicines Agency, Committee for Veterinary Medicinal Products, *Report of the CVMP on the Safety Evaluation of Steroidal Sex Hormones in particular for 17 β -Oestradiol, Progesterone, Altrenogest, Flugestone acetate and Norgestomet in the Light of New Data/Information made available by the European Commission*, EMEA/CVMP/885/99, December 1999, at p. 2 (Exhibit CDA-5). ("[T]he bioavailability of 17 β -oestradiol esters after oral administration is low (3% as unchanged 17 β -oestradiol), but it might be higher if estron, an estrogenic metabolite, is included".)

⁷⁸ See JECFA, *Toxicological evaluation of certain veterinary drug residues in food: prepared by the Fifty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Food Additives Series No. 43, (Geneva: WHO, 2000), Section 1.2.1 Absorption, distribution and excretion, at p. 45 (Exhibit CDA-11).

by JECFA. However, Dr. Boobis places the concept of bioavailability, and by extension the SCVPH analysis, in its proper context. He states:

However, low bioavailability does not necessarily increase the margin of safety (the ratio of ADI to actual exposure). This is because the effects of concern are usually determined following exposure by the route of interest, in this case oral. Hence, the ADI represents a "bioavailability adjusted" dose, just as the TMDI does. The consequence of this is that anything that increases bioavailability will reduce the margin of safety whilst anything that reduces bioavailability will increase the margin of safety. In the case of the natural hormones, changes in bioavailability are likely to be a consequence of changes in the enzymes of metabolism in the liver and/or small intestine.

163. Thus, as the ADI is a "bioavailability adjusted" dose, for the purposes of establishing the ADI, it matters not that the estimated bioavailability of the substance is later revised. The ADI is based on the dose that represents the NOAEL, together with appropriate safety factors. Thus, even if the SCVPH is correct that the bioavailability of the hormones at issue is higher than previously estimated, a conclusion that Canada contests, this has no impact on the ADI. The ADI could be called in question if, for instance, studies demonstrate that the bioavailability of oestradiol 17 β in residues in meat from treated cattle was higher than the bioavailability of the fine-particle oestradiol 17 β used in the studies that formed the basis of the ADI. However, the EC has presented no evidence to this effect. Indeed, the evidence points in the opposite direction.

(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]

164. Two experts, Dr. Boisseau and Dr. de Brabander, answer this question. Codex also answers a similar question posed to the international bodies (Question 15). The Codex definition of GPVD, with which both experts agree, is as follows:

Good Practice in the Use of Veterinary Drugs (GPVD) is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

165. In terms of Codex standards, guidelines and recommendations, Codex and Dr. de Brabander identify the *Codex Recommended International Code of Practice for Control of the Use of Veterinary Drugs (Codex Recommendations)*,⁷⁹ although Dr. de Brabander does so only in passing. Instead of discussing the *Codex Recommendations*, Dr. de Brabander extensively quotes from what appears to be a code of ethics and principles of conduct for the Federation of Veterinarians of Europe (FVE). Two points need to be made. First, the FVE code is not an international standard, guideline or recommendation. Second, a code governing ethical conduct is of limited relevance to risk assessments of veterinary drug residues in meat.

166. In contrast to the FVE, the *Codex Recommendations* addresses in detail such issues relating to the use of veterinary drugs as requirements for distribution, transport, and storage (e.g., temperature,

⁷⁹ Codex, *Recommended International Code of Practice for Control of the Use of Veterinary Drugs (Codex Recommendations)*, CAC/RCP 38 (Exhibit CDA-47).

humidity, light, *etc.*); requirements on handling and administration (*e.g.*, dose, method of use); withdrawal periods; disposal; and record keeping. Notably, the *Codex Recommendations* do not suggest that all veterinary drugs must be administered by a veterinarian:

[w]hen the administration of a medicine is not under direct veterinary supervision, it is therefore essential that, after the diagnosis, clear instructions should be provided on dose and methods of use, taking account of the competence of the user performing the work and ensuring that the correct calculation of, and the importance of adhering to, withdrawal periods is fully understood.⁸⁰

167. Regrettably, neither expert discusses the detailed provisions of the *Codex Recommendations* or whether this document sheds light on the EC's claim that GVP is "somewhat circular and hence problematic." Canada shares Dr. Boisseau's concern that the EC's comment is less than clear. This concern may flow from the fact that the EC appears to be questioning a well recognized international practice, employed by its own agencies.⁸¹ He posits that the EC means that the conditions of use of the veterinary drug may differ in a very significant way from one country to another. Here, Dr. Boisseau's answer to Question 45 is relevant.

168. Dr. Boisseau states that JECFA and other national authorities conduct risk assessments of veterinary drugs using studies in which the drug under review has been administered according to officially approved conditions of use (*i.e.*, labelled instructions). Thus, he suggests that adherence to GPVD is intricately linked to compliance with approved conditions of use (*e.g.*, storage, dose and method of use, withdrawal periods *etc.*).

169. The EC suggests that the circularity arises because "GVP is ... dependent upon what national authorities consider appropriate". This only becomes problematic if the conditions of use that underlie the studies relied upon by JECFA are more stringent than approved conditions of use at the national level. Consequently, it would be helpful if the experts could clarify whether the approved conditions of use in Canada for the hormones in question differ from the conditions of use underlying the studies that JECFA used to assess the safety of these hormones.

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?

170. Both Dr. Boisseau and Dr. de Brabander indicate that in conducting a risk assessment it is assumed that GVP is followed.⁸² Dr. Boisseau explains in greater detail that JECFA and other national authorities conduct risk assessments of veterinary drugs using studies in which the drug under review has been administered according to officially approved conditions of use. As discussed above, for the most part, use in accordance with GPVD means use in accordance with the approved conditions of use (*e.g.*, storage, transport, dose, method of use, withdrawal period).

171. As regards the second part of the Panel's question, Dr. Boisseau indicates that it is very difficult for risk assessors to identify all possible permutations of misuse and abuse. In terms of the risks that might arise from the failure to follow GPVD, Dr. Boisseau states:

⁸⁰ *Codex Recommendations*, at para. 5, p. 1.

⁸¹ In this regard, see Dr. Boobis' answer to Question 46, in which he states "appropriate residues studies are those obtained after the normal use of the hormones, *i.e.* in accordance with GVP. This is the policy of all agencies and organisations involved in such activities (*EEC, 1990; EMEA, 2005; FAO, 2006*)."

⁸² In the light of the answers to Question 44, Canada assumes that, when the Panel refers to GVP, it is actually referring to "good practice in the use of veterinary drugs" (GPVD).

It would not be appropriate also because it would not be ethical for the case where such data, being available, would lead to the conclusion of the risk assessment that, given a possibly wide margin of safety for a veterinary drug under review, the excess intake of residues associated with these misuses/abuses does not raise any problem of public health.

172. Canada requests that Dr. Boisseau clarify whether he is suggesting that, with respect to the growth-promoting hormones at issue, such a wide margin of safety has been incorporated into the risk assessment that any misuse and abuse is unlikely to give rise to adverse effects for human health?

173. Dr. de Brabander fails to respond to the Panel's actual question.

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?

174. Drs. Boobis, Boisseau and de Brabander respond to this question. Dr. Boisseau cites his answer to Question 45, implying he is of the view that the risks of misuse and abuse are not typically assessed by risk assessors such as JECFA. However, Dr. Boobis confirms that in several instances JECFA did consider the risks of misuse of some of the hormone growth promotants at issue, namely, zeranol and MGA.

175. Dr. Boobis also states that the point at which misuse and abuse is relevant in the risk assessment is at the risk characterization stage, during which potential exposure is compared with the ADI. He also states that, where appropriate, one could consider other potential exposure scenarios, such as the misuse and abuse of the substance in question.

176. Drs. Boobis and Boisseau appear of the view that it is not for JECFA to monitor compliance with GVP. Dr. Boisseau's answer to Question 45 above, is supported by Dr. Boobis' response to Question 62 where he states that:

[misuse and abuse] cannot be used as the basis for establishing MRLs. This is because whilst use according to GVP can be foreseen and regulated, it is not possible or appropriate to regulate any conceivable misuse or abuse, whether actual or hypothetical. Normally, the risk management strategy to deal with this is to ensure adequate surveillance of residues and to put in place a system of penalties for violation. This is the situation for veterinary drugs in all regions where they are subject to market authorisation, including the EU and the USA.

177. Therefore, to the extent that the EC is suggesting that JECFA's risk assessment is somehow flawed because it failed to assess potential misuse and abuse, the EC is fundamentally misconstruing JECFA's role.

178. Dr. de Brabander's answer is confusing and difficult to follow. First, he suggests that JECFA "denied" that there was misuse and abuse. Canada has carefully reviewed JECFA's reports and can find no example of JECFA "denying" such a possibility. In the light of the responses of the other experts, the Panel may wish to ask Dr. de Brabander to support this allegation. Second, he appears to draw illogical conclusions about the relationship between misuse and abuse and the establishment of MRLs. He states:

If other substances (like zilpaterol or ZMA etc ...) or uncorrect [*sic*] use of implants are used the principle of the establishment of MRLs by JECFA is certainly invalid [*sic*]

179. As Drs. Boobis and Boisseau explain, MRLs are established on the basis of the normal use of hormones, *i.e.*, in accordance with GVP, and are set independently of potential compliance issues. In the light of this evidence, Dr. de Brabander's conclusion is questionable, to say the least.

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?

180. Drs. Boisseau and de Brabander respond to this question. Dr. Boisseau, although acknowledging that he did not think that he was in a position to answer this question, indicates that in his view the main problem for the EC is that HGP's in North America are sold over the counter without veterinary supervision. He further states that "it is not possible to say that the European Communities took into account relevant control mechanisms with respect to GVP's in place in the USA and/or Canada" in its risk assessment.

181. On the other hand, in answering this question, Dr. de Brabander appears again to confuse concepts by suggesting that the very use of growth-promoting hormones is contrary to the principles of GVP. However, as the *Codex Recommendations* reveals, GVP establishes principles governing the use of veterinary drugs, but does not prescribe which substances can be used and for what purpose.

182. As to relevant control mechanisms, Dr. de Brabander again fails to answer the Panel's question and instead postulates that "any control mechanism, that is only based on audits and paper work will not prevent farmers to use either incorrect [*sic*] use of legal production aids either the use of other illegal growth promoters which are readily available in the US and Canada through the internet." Aside from the fact that Dr. de Brabander is straying from his area of expertise, the only evidence presented to support his assertion is a warning issued by Health Canada concerning athletic performance-enhancing products containing illegal anabolic steroids.⁸³ Although it is less than clear, Dr. de Brabander appears to imply that because anabolic steroids are used illegally in performance enhancing products in Canada, control mechanisms short of a complete ban would not prevent the misuse and abuse of HGP's. This logic is deeply flawed. A warning issued by Health Canada to protect Canadians from illegal anabolic steroids in bodybuilding drugs is hardly credible evidence of the existence or extent of the misuse and abuse of HGP's or an evaluation of relevant control mechanism.

183. Moreover, the illegal use of anabolic steroids by athletes has been a world-wide problem for decades. Much of the internet trade in illegal anabolic steroids originates in Europe, where controls over the distribution of these products are more lax.⁸⁴ The implication of Dr. de Brabander's logic is that, because these products are available in Europe through the internet, European farmers are misusing anabolic steroids in the husbandry of cattle.

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

⁸³ Health Canada, Advisory, *Health Canada advises consumers not to use unauthorized products containing anabolic steroids*, April 21, 2006; online at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_17_e.html.

⁸⁴ US Drug Enforcement Agency, *Anabolic Steroids, A Dangerous and Illegal Way to Seek Athletic Dominance and a Better Appearance*, "For purposes of illegal use there are several sources; the most common illegal source is from smuggling steroids into the United States from other countries such as Mexico and European countries. Smuggling from these areas is easier because a prescription is not required for the purchase of steroids. Less often steroids found in the illicit market are diverted from legitimate sources (e.g. thefts or inappropriate prescribing) or produced in clandestine laboratories"; online at: <http://www.deadiversion.usdoj.gov/pubs/brochures/steroids/public/public.pdf>.

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?

184. Although Drs. Boisseau, Boobis and de Brabander all provide answers, only the first two respond to the question posed by the Panel in a comprehensive fashion. These experts agree that the EC failed to assess risks to human health from residues of misplaced implants or improper administration. Dr. Boobis states directly that:

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.

185. For his part, Dr. Boisseau notes that the EC:

... is right to state that, in case of these different misuses/abuses, the exposure of consumers may be totally different. Once again, this situation is not specific to hormones as it applies also to all the veterinary drugs already assessed by JECFA, EU, USA or anywhere else in the world.

186. These responses support Canada's explanation that the EC has failed to evaluate the potential risks to human health from the misuse or abuse of the growth-promoting hormones at issue.⁸⁵ The EC has simply identified the possibility that misuse or abuse could occur without having evaluated its frequency or the potential risk to human health in the event it occurs. As Dr. Boobis states:

In my view, the potential hazards to the use of large quantities of the six hormones in dispute are those dependent on their endocrine activity, including cancer in hormonally responsive tissues. However, I should stress that this is their potential hazard. The potential risk, i.e. the probability that effects would occur, would depend on a number of factors. These include the magnitude of the exposure, the duration of the exposure and the life stage of the exposed individual. From the range of exposures likely from anticipated misuse or abuse the risks are likely to be very low.

187. In his response to Question 62, reviewing the EC's additional research conducted since 1997, Dr. Boobis further states:

Taking account of all of these factors, 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. Nor do they provide any indication that even such misuse and 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.⁸⁶

188. As Dr. Boisseau notes, the misuse and abuse of a substance could lead to exposure scenarios different from those contemplated in establishing an MRL. This applies to any veterinary drug, or indeed any substance for which an MRL is established. If it were sufficient for a WTO Member simply to raise the possibility, without any evaluation, of misuse and abuse as a justification for a ban

⁸⁵ Canada Rebuttal Submission, at paras. 107-111.

⁸⁶ Dr. Boobis, at p. 52.

on a substance, the obligation in Article 5.1 of the *SPS Agreement* to base an SPS measure on a risk assessment would be rendered illusory, and the work of international scientific risk assessment bodies, such as JECFA or the Joint Management Pesticide Committee, could be largely irrelevant. Mere assertions that misuse and abuse may occur without any evaluation of the factors outlined by Dr. Boobis on page 52 of his answers do not satisfy the requirements of a risk assessment as defined by the *SPS Agreement*.

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?

189. Only Dr. de Brabander responds to this question. He indicates that:

There are a large number of analytical methods available to control the use of the six hormones in dispute for growth promotion purposes. New methods are regularly presented in international conferences and in the open literature. In Europe a system of community reference (CRL) and national reference laboratories (NRL) is installed so that the analysis carried out by the field laboratories are kept up to the standards of the moment. If necessary I can provide the panel with a large number of methods but I don't think that is the purpose.

190. As it would be helpful to understanding the issues in dispute, the Panel may wish to ask Dr. de Brabander for a complete listing of available analytical methods to detect residues in meat and meat products for each of the hormones at issue as well as a complete description of the CRL and NRL networks to which he refers.

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?

191. Both Drs. Boisseau and de Brabander respond to this question. Dr. Boisseau makes a number of suggestions for addressing human health concerns arising from the failure by the exporting country to ensure compliance with GVP. He notes that a "[b]an is the last possible measure if all the other options have failed or have been proved ineffective."

192. In contrast, Dr. de Brabander states that there are no measures possible other than a complete ban that could address the risks arising from misuse and abuse. This remark appears inconsistent with his earlier statement in response to Question 49 that "[t]here are a large number of analytical methods available to control the use of the six hormones in dispute for growth promotion purposes."

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?

193. Both Drs. Boisseau and de Brabander respond to this question. Dr. Boisseau refers back to his answers to Questions 45 and 48, implying that, in his view, the misuse and abuse of hormones used for growth promotion do not call into question the potential applicability of Codex standards. Dr. Boisseau earlier commented that the establishment of ADIs and MRLs are based on an

assumption that GVP will be followed. Thus, in the unlikely event that GVP is not followed, the applicability of Codex standards is not put into doubt. Misuse or abuse may cause the residues of the substance in question to exceed the established MRL and may lead to exposure to the substance in excess of the established ADI, but it does not imply that the Codex standard is any less applicable. Questions of compliance with an MRL differ conceptually from whether the MRL is valid or applicable.

194. Unlike Dr. Boisseau, Dr. de Brabander appears to confuse the applicability of a Codex standard with the consequences of misuse and abuse. Then, he refers to "older" experiments upon which the ADIs and MRLs were based and suggests that "scientific knowledge on residues, their link with animal welfare and the impact on the environment has increased considerably." With respect, it is somewhat difficult to follow Dr. de Brabander's reasoning in this regard and it is less than clear how Dr. de Brabander's response addresses the Panel's question concerning misuse and abuse. To the extent that Dr. de Brabander suggests that the experiments on which the Codex ADI and MRL are based were "old" and no longer valid, he appears to be answering Question 34, on which Canada has already commented. Moreover, Dr. de Brabander's reference to his own study of the formation of boldenone has no bearing on the issue of misuse and abuse.

(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?

195. Drs. Boisseau and Boobis both agree with Canada that the scientific evidence relied upon by the EC does not demonstrate that there are adverse effects from the consumption of residues of hormones through meat from treated animals. Dr. Boisseau states that the EC did not carry out a risk assessment, but, rather, simply "provided scientific data and hypothesis supporting its worries" about the safety of the hormones. In particular, he confirms Canada's explanation of some of the flaws of the EC's risk assessment when he notes that the SCVPH should have:

integrated in its risk assessment the exposure of consumers to these hormones resulting from the consumption of hormone residues from animals which have not been treated by hormonal growth promoters and the [*sic*] from the daily production of these hormones by humans.

196. Dr. Boobis echoes this evaluation of the EC's risk assessment and its scientific evidence when he advises that "none of the information provided by the EC demonstrates the potential for adverse effects for humans" from meat from cattle treated with hormones. More specifically, he adds that:

[t]he studies on genotoxicity provide no convincing evidence of potential for harm in consumers. 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. As such, there would be no risk of such effects in human from such exposures. The 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. Other effects of the hormones that have been observed either in experimental animals or in exposed subjects occur at doses much higher than those to which consumers would be exposed via meat from treated

cattle. As such, there would be no risk of such effects in humans from such exposures.

197. For his part, Dr. Guttenplan seems to suggest, but does not explicitly state, that the EC has identified the potential for adverse effects. However, his main concern is based on the SCVPH's conclusion that pre-pubertal children have lower endogenous levels of hormones, itself based on data obtained principally by the Klein assay. As discussed in Canada's comments on Question 40, there are serious doubts about the validity of this assay. Dr. Guttenplan's endorsement of the EC's conclusions about adverse effects suffers from the same shortcomings as those conclusions themselves: they both rely on scientific methodologies that have not been validated.

198. All three experts provide useful advice on the evidence that would be required to demonstrate adverse effects, such as toxicological data (Dr. Boisseau), residue data that show that consuming treated meat leads to any change in circulating levels (Drs. Boisseau, Boobis and Guttenplan), and specific epidemiological studies (Dr. Boobis). It is important to note that none of them suggests that the EC has demonstrated such evidence currently exists.

Q53. Please comment on the statement by the European Communities that the natural hormones progesterone and testosterone are used only in combination with oestradiol 17 β 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]

199. Both Drs. Boisseau and Guttenplan, the only two experts that addressed this question, 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. They both acknowledge that it is oestradiol 17 β that is the most potent, with the addition of the others not significantly changing this potency such that the risk would increase. Therefore, once oestradiol 17 β has been demonstrated not to have adverse effects when used as a growth promoter, there is little risk that adverse effects would occur if used in combination with the other hormones.

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)]

200. Drs. Boisseau, Boobis and Guttenplan all advise that the acceptable level of risk reflected in Codex standards is that there is no risk of adverse effects if exposure to hormones is kept below the established ADI. In that sense, as Dr. Boobis points out, the acceptable level of risk reflected in the international standards is identical to that purportedly sought by the EC through its ban.

201. While Drs. Boisseau and Guttenplan both appear to suggest that the acceptable level of risk chosen by the EC is different than that embodied in the Codex standards, a close examination of their answers reveals that the difference to which they refer is that between theoretical risk and real risk, and not between acceptable levels of protection. That is, whereas the Codex standards indicate that there is no real risk if exposure is kept below the established ADI, the EC attempts to prevent even theoretical risk. Dr. Guttenplan confirms that the EC has not addressed the actual level of risk presented by consumption of meat from treated animals, only that there is a potential risk. Dr. Boisseau also advises that the EC will not accept "any risk, even theoretical [*sic*]".

202. Dr. Boobis expresses the issue in slightly different terms that lead to the same result. He advises that there is no difference between the two levels of risk (which are otherwise identical in that they accept zero risk to consumers of meat from treated animals) but there is a difference in how the evidence has been interpreted. On the one hand, in light of its conclusions that there is a threshold below which no adverse effects will result, Codex has adopted a standard that will not result in risk. On the other hand, in light of its conclusions that there is not a threshold below which adverse effects will not result, the EC has adopted a measure that it considers will not result in risk. To the extent that the experts in their answers to other question advise that the EC has not demonstrated that there is not a threshold, the EC has also not demonstrated that the international standards is insufficient to achieve its acceptable level of risk, which is identical to that embodied in the international standards.

203. The distinction made by the experts between theoretical risk and real risk is an important one in the context of this dispute also because it confirms that the sole reason for the EC to adopt a ban, rather than establish maximum acceptable exposure levels, was to avoid a theoretical risk, something that the Appellate Body has confirmed is not permissible under the *SPS Agreement*.

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]

204. Drs. Boisseau, Boobis and Guttenplan confirm that the EC did not evaluate additive risks. Dr. Boisseau's answer suggests that he believes the EC's "position of principle" (that it would not accept even any theoretical risk) prevented it from even trying to assess the "additive risks". Dr. Boisseau only partly answers the question, in that he only assesses the EC's decision not to compare hormone levels in treated meat versus untreated meat; he does not comment on the EC's failure to compare the effects of hormones from treated meat to the effects from all other sources of hormones, including endogenous production.

205. In the first sentence of his response, Dr. Guttenplan agrees that the EC did not evaluate "additive risks". It is not entirely clear, however, how his reference to the EC's comparison of exposure to hormones from treated meat and the background levels in prepubescent children is relevant to the evaluation of "additive risks". In fact, if anything the EC's selective evaluation of purported risks to sensitive populations from hormones from treated meat simply confirms that the EC has not evaluated "additive risks", because it has not conducted a similar evaluation of the risks posed by exposure from other sources of hormones, many of which are far greater than that from treated meat.

206. For his part, Dr. Boobis distinguishes between "aggregate risk" (risk resulting from the aggregate exposure from all sources of a single substance) and "cumulative risk" (risk resulting from the cumulative exposure from all substances with a common mechanism of toxicity) and then confirms that the EC evaluated neither kind of risk. Dr. Boobis explains that one way to assess the "aggregate risk" from exposure to exogenous sources of substances that are also produced endogenously is to determine the tolerable upper intake level taking into account endogenous production, then determine whether exogenous sources change the circulating levels of the substances in the body. JECFA has essentially done this for the natural hormones when it assessed the exposure from meat from treated animals relative to the circulating levels and found that the former fell within the normal variation of the latter.

207. Dr. Boobis acknowledges that a critical issue in assessing additive risks is whether there is a threshold below which adverse effects will not occur, something the EC argues is not the case with these hormones. As discussed previously, the EC's claim that there is no threshold for adverse effects from these hormones is simply not supported by the evidence. Therefore, its claim, from a "position of principle", that there are "additive risks" is similarly not credible in the absence of a quantitative evaluation of those risks. Indeed, the advice from the experts confirms Canada's identification of a critical flaw in the EC's claim that hormones from treated meat present an "additive risk": additive to what? In other words, what is the baseline risk from endogenous sources of hormones, or from other exogenous sources? Does exposure to hormones from meat from treated animals alter that risk? The EC does not ask, let alone answer, any of these questions, so it is difficult to see how its answer to the issue of additive risk can be legitimate.

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"?"

208. Two of the three experts who responded to this question, both of whom are quite familiar with the work of JECFA, advised that JECFA does take into consideration "additive risk" (covering what Dr. Boobis refers to as "aggregate risk" but not "cumulative risk"). The manner in which JECFA does so is similar to the process described above in Canada's comments on the responses to Question 55. That is, because there is such a wide "margin of safety" (Dr. Boisseau) between the exposure from hormones from treated meat and the aggregate exposure from all other sources (both endogenous and exogenous) and because the increase in aggregate exposure from consuming meat from treated animals was considered to be "trivial" (Dr. Boobis), there would be no "additional risk" over that from background levels.

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 17 β 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]

209. Drs. Boisseau, Boobis and Guttenplan indicated that the EC did not take into account in its risk assessment the risks that arise from the use of these hormones for therapeutic purposes. Both Drs. Boisseau and Boobis share Canada's difficulty in reconciling the EC's conclusion that there is no threshold below which there are no adverse effects from hormones from treated meat and its authorization of the use of these substances for certain purposes and not others. Dr. Boisseau considers it a "problem of principle", whereas Dr. Boobis suggests that the only way this is justified is if one assumes that there is a dose-response relationship, something the EC rejects. Dr. Guttenplan fails to support his observation that the EC's explanation for why it allows such use is "reasonable". On the whole, the experts' advice indicates that the EC is trying to have it both ways: that hormones are genotoxic for some purposes and not others.

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.

210. Drs. Boisseau, Guttenplan and Boobis all expressed in their own ways some difficulty with this statement by the EC. Dr. Boisseau suggests (with reference to his answer to Question 55) that this constitutes simply a "position of principle", one not supported by evidence that there are additive risks from higher doses of these hormones. Dr. Guttenplan simply offers that it is "indeed a very weak statement". His further suggestion that it is nonetheless better than an estimate of risk that is "wildly inaccurate" only reinforces Canada's concern that there is simply no basis for the EC to draw such a conclusion. Dr. Boobis confirms again that this statement is not supported by the evidence in that "within quite broad limits, higher exposure would not result in an increase in risk". Considering that hormone intake from meat from treated cattle represents only 1.5% of the ADI (the level below which there is no risk), it simply cannot be "inferred from the available scientific data" that exposure to more residues from meat from treated animals will lead to greater risk.

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]

211. While the three experts that responded to this question all acknowledge that there can be adverse effects on the immune system from hormonally active substances, they all confirm that there is no scientific evidence that such effects will occur from exposure to doses of hormones that would be expected from residues in meat from treated animals. Dr. Boobis points to the "margin of safety" inherent in the dose relative to the background level; Dr. Boisseau indicates that the EC has not conducted the "quantitative risk assessment" that would be required to demonstrate risk from what are known to be dose-dependent adverse effects; and Dr. Guttenplan simply cites the absence of "definitive studies" (although he could have just as easily referred to the absence of "any studies") of low dose adverse immune system effects. All of the experts therefore confirm that for the EC to demonstrate that there are risks of adverse effects to the immune system from hormones from treated meat, it would have to demonstrate that such exposure would surpass the threshold at which such adverse effects would occur. It has not.

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?

212. Drs. Boisseau, Boobis and Guttenplan all indicate that the EC did not demonstrate that the potential for adverse effects differs depending on the route of administration. Only Dr. Boobis indicates that there may be a difference in effect as a result of misuse and abuse of implants, which would not occur in feed additives. However, he only acknowledges that the level of the exposure may be greater, and not that the level of risk of adverse effect necessarily would be greater. For the level of risk of adverse effects to be different, the exposure from one source of administration or the other would need to exceed the ADI, something that is quite unlikely to happen.

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?

213. Both Drs. Boobis and Guttenplan indicate that sufficient scientific evidence was available to the EC to conduct a risk assessment of the five other hormones. Dr. Boisseau indicates that he is unaware of what the EC had available to it at the time, but goes on to suggest that it is never possible to eliminate all scientific uncertainty, and that the EC could have obtained any information it felt it did not have. Dr. Guttenplan specifically, and Dr. Boobis through reference to his other answers, both point to work done by JECFA as establishing that the data are complete enough to conduct risk assessments. It also seems to be the case, especially from Dr. Boobis' reference to his other answers, that since there is sufficient evidence to demonstrate the safety of oestradiol 17 β , which is considered to be the more potent substance, the same type of data and principles of analysis that demonstrate the safety of this substance indicate that the other five hormones will also be safe.

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?

214. While Drs. Boisseau, Boobis and Guttenplan all indicate that new scientific evidence has raised new and interesting issues, they do not agree that this evidence suggests important gaps in the understanding of the safety of these substances. Dr. Boisseau does not believe that these new data are contrary to previous conclusions or that they make it impossible to conduct a risk assessment. Dr. Guttenplan suggests some new areas of potential study, but some of them are already answered (see, for example, Dr. Boobis' review of the effect of consuming meat from treated animals on blood levels of oestrogen); some of them are not necessary for the completion of a risk assessment; and at least one of them (epidemiological studies of consumption of treated versus non-treated meat) will never be able to demonstrate the linkages that Dr. Guttenplan would like to see (see discussion of confounding factors above). Dr. Boobis provides the most comprehensive assessment of the new scientific data, and addresses each and every study that the EC claims raise new scientific issues. As a result of his review, he concludes that the additional information "was often not definitive, sometimes it was not relevant, in some instances it confirmed or expanded upon previous knowledge".

III. COMMENTS ON INTERNATIONAL ORGANIZATION REPLIES

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?

215. Canada has no comments to make at this time.

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

216. Canada has no comments to make at this time.

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.

217. See Canada's comments on the experts' answers to Question 3.

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)]

218. See Canada's comments on the experts' answers to Question 4.

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.

219. See Canada's comments on the experts' answers to Question 5.

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.

220. See Canada's comments on the experts' answers to Question 6.

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]

221. See Canada's comments on the experts' answers to Question 7.

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]

222. See Canada's comments on the answers from the experts to Question 37.

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

223. See Canada's comments on the answers from the experts to Question 8.

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.

224. See Canada's comments on the answers from the experts to Question 8.

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]

225. See Canada's comments on the answers by the experts to Question 9.

Q12. In para. 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?

226. See Canada's comments on the answers from the experts to Question 10.

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]

227. JECFA confirms in its response that "[u]npublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA", and that "confidential data will either be returned to the submitter at the submitter's expense or destroyed after the evaluations have been completed."

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

228. Canada has no comments to make at this time.

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

229. See Canada's comments on the responses from the experts to Question 44.

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?

230. Canada has no comments to make at this time.

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?

231. JECFA confirms that, with the addition of a reference to the 66th JECFA meeting held 20-28 February 2006, at which meeting JECFA further deliberated on the MRLs previously proposed for MGA, Exhibit CDA-32 is complete.

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?

232. See Canada's comments on the answers by the experts to Question 33.

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]

233. JECFA's response states that "[t]he re-evaluations of compounds follow the same procedure as an evaluation performed for the first time, with clear identification of the new data that were assessed." See also Canada's comments on the answers from the experts to Question 33.

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 paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

234. See Canada's comments on the answers by the experts to Question 33.

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

235. Canada has no comments to make at this time.

Q22. Who are the members of the IARC?

236. Canada has no comments to make at this time.

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

237. Canada has no comments to make at this time.

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?

238. The Panel may wish to request further explanation from IARC regarding the considerations that determine the classification by IARC of a substance as belonging to Group 1, 2A or 2B, as well as the consequences or implications of such a classification.

Q25. Which of the six hormones at issue in this dispute (oestradiol 17 β , 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?

239. IARC's response states that it has evaluated the three natural hormones but not the three synthetic hormones. IARC's evaluation and classification of the three natural hormones appears not to have taken into account the different potential sources of these hormones and the different potential levels of exposure of individuals. Thus the kind of risk assessment that was conducted by JECFA was apparently not carried out by IARC. IARC does not respond to the question about the specific risks from exposure to residues of hormones in meat from treated animals.

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?

240. IARC's response to Question 26 is the same as that to Question 25.

IV. CONCLUDING COMMENTS

241. The experts and international bodies have provided extensive advice on the scientific and technical matters at issue in this dispute. The experts' responses exhibited general agreement that the scientific evidence and information does not support the conclusions of the EC's evaluation of these six hormones. While this is the case for most of the issues addressed by the experts, several issues that are central to the Panel's review of the EC's evaluation warrant specific mention.

242. In particular, the experts indicate that the scientific evidence does not support the following conclusions:

- that all or some of the hormones (but in particular, oestradiol 17 β) present a risk of adverse effects (such as genotoxicity) that do not exhibit an exposure dose below which they will not occur (*i.e.*, a threshold);
- that exposure to the hormones from residues in meat from treated animals will be so significant in proportion to the endogenous hormone levels present in certain sensitive populations such that adverse effects will occur;
- that the exposure from this single source of hormones is sufficiently "additive" to the exposure from all sources of hormones to increase the risk of occurrence of adverse effects;
- that the failure to follow GVP will result in exposure to the hormones at doses capable of causing adverse effects and that the hormones are administered in Canada in a manner that fails to follow this GVP; and
- that the scientific evidence is insufficient to conduct an assessment of the safety of the five hormones other than oestradiol 17 β .

243. Canada looks forward to meeting with the experts and to the opportunity to discuss these and other scientific and technical issues in more detail.

ANNEX F-5

**COMMENTS BY CANADA TO THE COMMENTS
OF THE EUROPEAN COMMUNITIES ON THE REPLIES OF THE
SCIENTIFIC EXPERTS, CODEX, JECFA AND IARC
TO QUESTIONS POSED BY THE PANEL**

(12 July 2006)

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I. INTRODUCTION

1. Canada is pleased to have this opportunity to comment on the comments by the European Communities (EC) on the responses by the experts and by JECFA, Codex and IARC. Before turning to comments on the specific responses, several issues of a general nature raised by the EC warrant mention.

2. First, the EC suggests in many of its comments that it is either Canada or the experts that need to demonstrate that adverse effects will not arise from consuming residues of hormones in meat from treated animals.¹ It is important to recall that it is the EC that has adopted bans on these hormones as growth promoters on the basis that they cause adverse effects, and it is the EC that has brought this case against Canada, alleging that these bans are justified under the *SPS Agreement*. Any suggestion

¹ For example, see EC Comments on the Replies by the Panel Experts, in relation to Questions 18, 20 and 59 (EC Comments).

by the EC that the burden is on Canada to prove that adverse effects will not arise runs contrary to the applicable WTO rules on the allocation of burden of proof. Similarly, any suggestion by the EC that the experts must demonstrate that such adverse effects will not arise demonstrates a misunderstanding of the role of the experts in these proceedings.

3. Therefore, it is the EC – and not Canada or the experts – that must demonstrate that it has scientific evidence that supports its claim that adverse effects will arise from consuming residues of hormones in meat from treated animals. Consequently, the focus of the discussion should not be on the manner of adoption of the international standards and their scientific underpinnings but rather on the EC's opinions and whether they meet the requirements of the *SPS Agreement*.

4. Second, the EC makes a number of assertions in its comments that are accompanied by citations of articles that have not been filed as exhibits. Canada has been able to locate some of the articles, but not all of them and, accordingly, limits its comments to those it has been able to locate. However, to the extent that the EC refers to this material in relation to claims about scientific evidence that it is making for the first time, and then fails to provide the supporting material, the claims remain no more than unsupported assertions that should be given no weight by the Panel.

5. Third, in its comments on certain experts' responses, the EC questions the relevance of the views of Dr. Boisseau and Dr. Boobis because, according to the EC, they did not carry out "experiments on hormones" and publish related scientific papers.² The *curricula vitae* of both these experts, which demonstrate extensive experience in the risk assessment of many veterinary drugs as well as other chemicals, and the quality of their replies, speak for themselves. While it is the EC's prerogative to disagree with the answers provided by any of the experts, there can be no doubt about the professional competence of Dr. Boisseau and Dr. Boobis that underlies their answers to the Panel's questions.

6. Fourth, the EC tries to impugn the comments from Codex and JECFA, but not those from IARC, by questioning the legality of the transmittal of these comments by the Codex and JECFA Secretariats respectively to the Panel, without having complied with internal procedures that were not identified by the EC. It would not be appropriate for the Panel to inquire into the question of compliance with the internal rules of other international bodies. Also, the information provided by the Codex and JECFA Secretariats are matters of public record. In any event, it would be open to the EC to take any steps it deems appropriate within Codex and JECFA to deal with this issue.

7. Canada will address the EC's comments on the responses of the international bodies in Part III of this submission.

8. And finally, given the short time-frame for the preparation of these comments, the absence of comments by Canada on certain assertions by the EC should not, of course, be construed as agreement with such assertions.

II. COMMENTS ON THE COMMENTS FROM THE EC ON THE RESPONSES FROM THE EXPERTS

A. GENERAL DEFINITIONS

9. In its comments on the experts' responses to **Question 1**, the EC quibbles with Dr. Boisseau's definition of the hormones at issue in this dispute. To the extent that the issues raised by the EC are relevant, Canada will address them below.

² *Ibid.*, Questions 2, 17, 21 and 42.

10. The EC's attempt to discredit Dr. Boisseau's response to **Question 2** by referring to his earlier indication of which questions he intended to answer is unjustified. Other experts, such as Dr. Cogliano and Dr. de Brabander, answered questions that they did not originally indicate they would answer; some of them in the end declined to answer questions they had earlier indicated they would answer. That is the experts' prerogative and nothing more should be read into an expert responding or not responding to particular questions.

B. RISK ASSESSMENT TECHNIQUES

11. In its comments on the experts' responses to the Panel's Questions in this section (**Questions 3-12**), the EC raises several issues that warrant comment at this stage. These are:

- the meaning of the phrase "risk assessment techniques developed by the relevant international organizations", as found in Article 5.1 of the *SPS Agreement* and its relevance to this dispute;
- the relevance of the different mandates of the European Medicines Agency's Committee for Veterinary Medicinal Products (CVMP) and the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH);
- the distinction between risk assessment and risk management;
- the meaning of "no appreciable risk";
- the distinction between qualitative and quantitative risk assessments and the relevance of this distinction to the meaning of "risk assessment" as found in the *SPS Agreement*;
- the existence of scientific uncertainty; and
- the relationship between weight of evidence and minority science.

"Risk Assessment Techniques" in Article 5.1 of the SPS Agreement

12. In its comments on the responses to **Questions 3, 4 and 6**, the EC attempts to dismiss the various international guidance documents identified by the experts and JECFA and Codex as being relevant to the conduct of veterinary drug risk assessments. In doing so, the EC distorts the meaning of the phrase "risk assessment techniques developed by the relevant international organizations" in Article 5.1 of the *SPS Agreement*.³ The thrust of the EC submission is that unless an international guidance document is formally adopted by Codex it is not "legally binding" and therefore cannot constitute a "risk assessment technique" under Article 5.1 and is irrelevant.⁴ However, the EC's line of reasoning is misguided. The question is not whether the "risk assessment techniques" are "legally binding" but whether the "risk assessment techniques" assist in determining whether the risk assessment at issue is "appropriate to the circumstances." For a risk assessment to be "appropriate to the circumstances", the WTO Member must "tak[e] into account the risk assessment techniques...". Failure to do so suggests that the assessment at issue is not "appropriate to the circumstances".

³ Article 5.1 of the *SPS Agreement* reads in full "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 or health, taking into account risk assessment techniques developed by the relevant international organizations."

⁴ See EC Comments, Questions 3, 4 and 6.

13. To the extent that the EC is suggesting by the phrase "legally binding" that "risk assessment techniques" must be formally established by one of the international organizations listed in Annex A(3) as a "standard, guideline and recommendation", the EC is incorrect. Had the Members intended such an effect, then they would have used "standard, guideline and recommendation" in Article 5.1. The fact that they did not implies this is not the case. The use of the term "technique" suggests that the treaty drafters were referring to the technical aspects of risk assessment methodology. Some "techniques" may be embodied in a formally established "standard, guideline, and recommendation", while others may not. The "risk assessment technique" must be "developed by the relevant international organization." Without question, Codex is a "relevant international organization". Given that Codex relies on the work of JECFA to conduct risk assessments and develop risk assessment techniques for food additives, contaminants and veterinary drugs, it can be inferred that JECFA is a "relevant international organization" for the purposes of Article 5.1.

14. In this case, "risk assessment techniques" developed by Codex include the four steps of the risk assessment process (hazard identification, hazard characterization, exposure assessment and risk characterization). Those developed by JECFA are embodied in EHC 70⁵ and the JECFA Procedures.⁶ More specific to this case are techniques such as the assessment of the quality and quantity of available study data, determination of pivotal studies and the NOAELs (No Observed Adverse Effects Levels), the conduct of the dose-response assessment, the selection of appropriate safety factors and the establishment of ADIs (Acceptable Daily Intakes). Therefore, assessments of veterinary drugs that fail to take into account these techniques are not, *prima facie*, "appropriate to the circumstances" and, therefore, do not satisfy the requirements of Article 5.1 and the definition of risk assessment in Annex A(4).

Relevance of the different mandates of the CVMP and SCVPH

15. In its comments on responses to **Question 3**, the EC's attempt to discredit Dr. Boisseau's advice concerning the CVMP's ability to assess pharmacologically active substances used in veterinary medicine "without any written guideline about risk assessment" is confused and illogical. The EC appears to imply that techniques used by the CVMP in conducting risk assessments are not applicable to the work of the SCVPH on the basis that the SCVPH's mandate differs from that of the CVMP. This appears to be an indirect attempt to explain the differing conclusions reached by these committees in relation to adverse effects caused by the use of hormones in animal husbandry. However, the fact that these two committees assess different uses of the same substances has no bearing on the nature of the risk assessment techniques employed. For instance, the techniques adopted to determine whether oestradiol 17 β is genotoxic apply regardless of the use to which the substance will be put. If oestradiol 17 β , when used for therapeutic purposes, has a dose threshold, it is illogical to conclude that it does not have a dose threshold when used for growth-promotion purposes. The EC cannot escape from the CVMP's conclusion that oestradiol 17 β is not genotoxic by referring to different committee mandates.

Risk Assessment/Risk Management

16. The EC attempts, in its comments on responses to **Question 5**, to dismiss all the explanations provided by the experts of the three components of "risk analysis" by reiterating its previous arguments concerning the differing scope of, on the one hand, risk assessment as defined by the *SPS Agreement*, and, on the other hand, risk assessment as a component of Codex's risk analysis. As

⁵ International Program on Chemical Safety, *Principles for the Safety Assessment of Food Additives and Contaminants in Food, Environmental Health Criteria 70* (Geneva: WHO, 1987) (EHC 70) (Exhibit CDA-43).

⁶ JECFA, *Procedures for Recommending Maximum Residue Limits – Residues of Veterinary Drugs in Food (1987 – 1999)* (Rome: FAO/WHO, 2000) (JECFA Procedures) (Exhibit CDA-44).

Canada has explained in detail in its Rebuttal Submission,⁷ the EC is attempting to insulate its SPS measure, *i.e.*, its ban on all meat and meat products derived from treated animals, from Panel review by suggesting that the "wider" risk assessment contemplated by the *SPS Agreement* includes risk management considerations and that risk management is *a priori* non-reviewable because it is related to a WTO Member's autonomous right to set its appropriate level of protection.

17. As Canada explained, the EC cannot escape the obligation in Article 5.1 of the *SPS Agreement* to base its measure on a risk assessment by claiming that a component of the risk assessment includes non-reviewable risk management considerations. The Appellate Body's statement that Article 5.1 was "intended as a countervailing factor in respect of the right of Members to set their appropriate level of protection"⁸ implies that risk management and the autonomous right of each WTO Member to set its level of protection cannot be used to avoid the obligation in Article 5.1.

The concept of "Appreciable Risk"

18. The EC arguments concerning "appreciable risk" are a direct challenge to one of the cornerstones of modern risk assessment techniques widely employed by risk assessment bodies at both the national and international level. The EC attempts to discredit this concept by asserting that it is "subjective", "qualitative" and "unspecific".⁹ However, these arguments reflect a profound misunderstanding of this concept and its role in the risk assessment process.

19. The phrase "without appreciable risk" is found in Codex's definition of ADI: "an estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk".¹⁰ To understand what is meant by "appreciable health risk", or "appreciable risk", one must consider the risk assessment process as a whole. On the basis of detailed scientific experimentation, observation and analysis of empirical data, a NOAEL is set for each observed adverse effect. The NOAEL represents the dose level at or below which no adverse effect is empirically observed or measured in the target organism.

20. The NOAEL is then adjusted by safety factors to derive the ADI. If no effect is observed, then, logically, there is no observable or empirically ascertainable risk. Appreciable, in the sense used in the ADI, means observable, ascertainable or identifiable. Thus, far from being "subjective" or "qualitative", as the term is used by the EC, the identification of a lifetime daily intake that is "without appreciable risk" is based on quantitative scientific experiments that lead to objective, measurable observations. Indeed, the very purpose of the risk assessment methodology used by JECFA and Codex is to identify quantitatively the point at which risks are not observed or ascertained.

21. When "appreciable risk" is properly understood, the EC's comments do not make sense. An ADI based on "no appreciable risk" implies that there is no scientifically identifiable or ascertainable risk if the daily intake is equal to or below the ADI. Of course, the ADI does not eliminate the theoretical uncertainty that always exists as "science can *never* provide *absolute* certainty that a given substance will not *ever* have adverse health effects".¹¹ However, this theoretical uncertainty, or hypothetical risk, is not the kind of risk that, under Article 5.1 of the *SPS Agreement*, is to be assessed.¹² Thus, assuming that good veterinary practice is followed, the difference between the level of risk inherent in an ADI and the EC's purported "zero risk" level of protection, is not ascertainable

⁷ Canada Rebuttal Submission, at paras. 55-65.

⁸ *EC – Measures Concerning Meat and Meat Products (Hormones)*, Report of the Appellate Body, WT/DS26/AB/R, WT/DS48/AB/R, adopted February 13, 1998, at para. 177 (*EC – Hormones*).

⁹ See EC Comments, Questions 8, 16, 25 and 54.

¹⁰ See Codex's reply to Panel IO Question 9 [emphasis added].

¹¹ *EC – Hormones*, at para. 186 [emphasis in original].

¹² *EC – Hormones*, at para. 186.

or identifiable risk, but theoretical or hypothetical and is not the kind of risk to be assessed under Article 5.1.

Quantitative and Qualitative Risk Assessments

22. In its comments on the responses to **Questions 11, 16 and 36**, the EC attempts to neutralize the evidence of Dr. Boisseau and Dr. Boobis concerning the distinction between quantitative and qualitative risk assessments by claiming that the Appellate Body has confirmed that qualitative risk assessments are "acceptable" under the *SPS Agreement*. However, as Canada explained in its Rebuttal Submission, although the Appellate Body concluded that a risk assessment need not establish a "minimum magnitude of risk" in order to be consistent with Article 5.1, it did not discuss qualitative and quantitative risk assessments, writ large.¹³ Thus, the EC's attempt to deduce from this conclusion the more general proposition that a qualitative risk assessment is acceptable, *a priori*, under the *SPS Agreement* distorts the conclusions of the Appellate Body. The critical question is whether the risk assessment at issue evaluates the potential for adverse effects in a manner "appropriate to the circumstances ... taking into account risk assessment techniques developed by the relevant international organizations". If the nature of the substance is such that no threshold for adverse effects can be established, then a dose-response assessment is not necessary. However, when scientific evidence demonstrates, as it does in this case, that a dose threshold below which no adverse effects occur can be established for the substance in question, a risk assessment that fails to include a quantitative dose-response assessment would not be "appropriate to the circumstances."

The existence of Scientific Uncertainty

23. In its comments on the experts' responses to **Question 12**, the EC attempts to impugn the use of safety factors to address certain types of scientific uncertainty.¹⁴ It suggests that where new scientific evidence casts doubt on previous scientific conclusions, safety factors cannot adequately compensate for the resulting uncertainty. Whether this assertion is correct as a matter of principle is debatable; in any event, it does not apply in this case. As the experts have amply demonstrated, the "new" scientific evidence referred to by the EC does not call into question the scientific conclusions concerning the potential for adverse effects from residues of hormones in meat from treated cattle, particularly conclusions relating to their carcinogenic potential. The EC is simply trying to create scientific uncertainty where there is none.

The relationship between "weight of evidence" and minority scientific opinion

24. In its comments on the experts' responses to **Question 12**, the EC highlights Dr. Boobis's use of the term of "weight of evidence" and seeks to equate the term with "mainstream scientific views". The EC further suggests that using a "weight of evidence" approach forces WTO Members to dismiss or ignore minority scientific views. These arguments reveal a misunderstanding of the term as used in the context of risk assessments. The term "weight of evidence" is a term of art used to characterize the interpretation of all scientific evidence relevant to the causal hypothesis under review, in drawing conclusions about causal relationships. Not all scientific evidence will be of equivalent importance, or weight, in providing information about presence or absence of a causal relationship. A "weight of evidence" approach involves assessing the relative strength and conclusiveness of all relevant data, including the quality of testing methods, size and power of study design, consistency of results across

¹³ Canada Rebuttal Submission, at paras. 81-82. Also see *EC – Hormones*, Report of the Appellate Body, at para. 186.

¹⁴ The EC does not appear to suggest that the use of safety factors is inappropriate to address the scientific uncertainty arising from inter-species and intra-species variability. Had it done so, it would be challenging a fundamental risk assessment technique widely employed by its own scientific committees and regulators.

studies, and biological plausibility of exposure-response relationships and statistical associations. It is not equivalent to "mainstream scientific views", but is a process that should underpin the formation of scientific opinions generally, be they mainstream or minority, in order to ensure that they are scientifically sound. Dr. Boobis appears to use "weight of evidence" to indicate that the EC conclusions were not based on an evaluation of all pertinent scientific evidence, including an assessment of the relative strength of that evidence.

C. ASSESSMENT OF OESTRADIOL 17B

25. The EC makes several comments on the experts' responses to **Questions 13** and **14** that warrant further comment. These include the EC's: 1) inaccurate and misleading descriptions of the adverse effects it purports to have identified; 2) exaggeration of the role of epidemiological studies in risk assessments of the kind appropriate to these circumstances; 3) repeated attempt to embellish scientific results to demonstrate *in vivo* genotoxicity from oestradiol 17 β ; and 4) unjustified reliance on several new scientific studies and its criticism of the experts for failing to take these into account.

Inaccurate and misleading descriptions of the purported adverse effects

26. In response to the advice from the experts under **Question 13** that the SCVPH opinions do not amount to a risk assessment, the EC makes several confusing assertions about the nature of the adverse effects that it purports to have identified. In particular, on several occasions it uses interchangeably the terms 'carcinogenicity' and 'genotoxic effect', linking them both to the interaction of these hormones with hormonal receptors.¹⁵ The EC's description of the issues is both wrong and misleading, so for purposes of restoring clarity to the issues it is useful to restate the basic controversy related to the potential carcinogenicity of these hormones and to summarize the advice of the experts.

27. The claim made by the EC is that oestradiol 17 β is carcinogenic because it both initiates tumours and promotes tumour growth, the former through a hypothesized genotoxic effect and the latter through interaction with hormonal receptors.¹⁶ To the extent that the international scientific authorities and the experts consulted by the Panel agree with the general proposition that oestradiol 17 β is carcinogenic, they unanimously attribute this effect exclusively to its interaction with hormone receptors.¹⁷ At the same time, the experts have confirmed again that there is no scientific evidence demonstrating that oestradiol 17 β initiates tumours through a genotoxic effect.¹⁸

28. The distinction between these two different mechanisms of carcinogenicity is an important one because the findings of receptor-mediated carcinogenicity by JECFA, IARC and other scientific authorities have been exclusively attributed to circumstances involving high dose exposure to hormones, something that is clearly not a factor in exposure to dietary sources of hormones, including that from residues in meat from treated cattle. The EC's careless interchanging of the mechanisms of action and the role of dose is simply an attempt to confuse the scientific evidence related to carcinogenicity.

¹⁵ See EC Comments, at p. 12 (Question 13).

¹⁶ The EC's claim in its comments that the "genotoxic effect of oestradiol 17 β is associated with its hormonal activity" [emphasis added] is simply nonsensical. *Ibid.*

¹⁷ Canada's Rebuttal Submission, at paras 90-95.

¹⁸ The EC's statement that the "carcinogenicity of estrogens is primarily due to oxidative stress/DNA adduct formation caused by the catechols [*sic*] metabolites of estrogens" is unsupported by any of the evidence submitted by the EC and is not supported by the experts. *Ibid.*

Role of epidemiological studies

29. The EC on several occasions in its comments relies on the results of epidemiological studies,¹⁹ in particular those conducted or sponsored by IARC, as well as those on which the 2002 US Report on Carcinogens was based, as the central support for its claims that it has identified and evaluated adverse effects from the consumption of meat from treated animals. In doing so, the EC vastly overestimates the role of epidemiological studies in risk assessments of the kind required in these circumstances, that is, of exposure to substances in such small doses.

30. None of the studies cited by the EC purports to identify a relationship between cancer and residues of hormones from meat derived from treated animals. It is true that in 1987 IARC classified steroidal oestrogens as a Group I carcinogen on the basis of observed relationships between cancer and treatments using high doses of oestrogens.²⁰ However, the Appellate Body has already specifically rejected the claim that this classification demonstrates anything about the substances at issue here. In upholding the findings of the panel, it found that the IARC Monographs:

constitute general studies which do indeed show the existence of a general risk of cancer [from oestrogen]; but they do not focus on and do not address the particular kind of risk here at stake - the carcinogenic or genotoxic potential of the residues of those hormones found in meat derived from cattle to which the hormones had been administered for growth promotion purposes -- as is required by paragraph 4 of Annex A of the *SPS Agreement*.²¹

31. Since that time, IARC further classified postmenopausal oestrogen therapy²² and combined oral contraceptives²³ as Group I carcinogens, again on the basis of observed relationships between cancer and these treatments. However, what all of these classifications have in common is that they involve prolonged, high dose exposure to various forms of oestrogen. Therefore, the reasoning used by the Appellate Body in the above excerpt applies equally to the EC's invocation of more recent IARC findings, as well as to any use of other findings that are based on the results of epidemiological studies.

32. As the experts have confirmed,²⁴ it is simply not possible to draw specific conclusions about adverse effects from residues of hormones in meat from treated animals on the basis of epidemiological studies. For that reason, these kinds of studies have limited usefulness in a risk assessment of the nature required to justify the EC's measure. They may help in identifying possible adverse effects, but they reveal nothing about the potential for occurrence of such adverse effects from a single dietary source of hormones.

33. The EC's claim that epidemiological studies, such as those on which IARC's classification of oestrogen as a carcinogen are based, support its claim is all the more surprising in light of its subsequent comment on Dr. Guttenplan's response to **Question 13**. The EC comments that it:

¹⁹ See EC Comments, at pp. 12 (Question 13), 20 (Questions 20), 23 (Question 23) and 24 (Question 24).

²⁰ *EC – Hormones*, Report of the Appellate Body, at paras. 199-200. Also, the note attached to IARC's classification indicates that this "evaluation applies to the group of compounds as a whole and not necessarily to all individual compounds within the group" (online: <http://monographs.iarc.fr/ENG/Classification/crthgr01.php>).

²¹ *Ibid.*, at para. 200.

²² IARC, Vol. 91, Monograph No. 2, Section 5, *Combined Estrogen-Progestogen Menopausal Therapy* (Lyon, France: 2005) (Exhibit CDA-48).

²³ IARC, Vol. 91, Monograph No. 1, Section 5, *Combined Estrogen-Progestogen Contraceptives* (Lyon, France: 2005) (Exhibit CDA-49).

²⁴ See experts' responses to Question 26.

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.

34. In this statement, the EC acknowledges the absence of epidemiological studies that demonstrate that there are risks from consuming residues of hormones from meat from treated animals. More importantly, the EC acknowledges the significant limitations of such studies to support such a conclusion.

Embellishment of scientific evidence related to in vivo genotoxicity

35. In its comments on the experts' responses to **Questions 7, 13 and 18**, the EC refers to several scientific studies in support of its claim that oestradiol 17 β can cause genotoxicity *in vivo*. It is important to recall that the experts are very clear that evidence of *in vivo* genotoxicity, as well as evidence that the mode of action of genotoxicity is of a type that does not exhibit a threshold, are required to confirm findings of *in vitro* genotoxicity before it can be concluded that such genotoxicity is relevant to the development of cancer.²⁵ The studies cited by the EC do not satisfy these requirements.

36. In the first study referred to by the EC, by Bhat *et al.*, the authors conclude that their data "provide evidence that oxidant stress plays a crucial role in estrogen-induced carcinogenesis". However, as Dr. Boobis has indicated in his responses, oxidative stress as a genotoxic mode of action is of a type that is universally considered to demonstrate a threshold response, due to the "efficiency of endogenous antioxidant systems".²⁶ Therefore, this study does not demonstrate anything that was not already known, but simply confirms that genotoxicity can result from overwhelming the antioxidant systems with high doses of oestradiol 17 β .

37. In its comments on the responses to **Questions 16, 18 and 62**, the EC introduces, also for the first time, a review by Yager and Davidson that the EC claims confirms that the "evidence is now sufficient to support a role for the estrogen metabolites which include the genotoxic, mutagenic estrogen quinones in estrogen carcinogenicity." The first point is that this article is only a review of other studies so provides no new evidence on its own. Second, like the studies conducted by Bhat *et al.*, this review postulates an oxidative stress damage pathway for genotoxicity, which, as noted above, is considered to have a threshold.

New scientific material cited by the EC and the role of the experts' advice

38. In its comments on the experts' replies to **Questions 13 and 14**, the EC cites a number of additional studies to support claims made in its comments and in earlier submissions. Some of these studies are introduced by the EC for the first time in its comments, very few of them were considered by the SCVPH in its opinions, and most of them do not support the specific claims made by the EC about adverse effects arising from residues of hormones in meat from treated animals.

39. The EC introduces several new studies in an apparent misunderstanding of what the experts had been asked to do. In its comments on the responses to **Question 13** concerning whether the EC

²⁵ See experts' responses to Questions 16, 18 and 19.

²⁶ Dr. Boobis's response to Question 16. See also EFSA, *Opinion of the Scientific Committee on a Request from EFSA Related to a Harmonised Approach for Risk Assessment of Substances which are both Genotoxic and Carcinogenic* (Request No. EFSA-Q-2004-020, adopted October 18, 2005) (*The EFSA Journal*, 282, 1-31, 2005), at p. 18 (Exhibit CDA-46).

opinions evaluate the potential occurrence of adverse effects (a question that specifically asks the experts for advice on the 1999, 2000 and 2002 SCVPH opinions), the EC raises two entirely new claims about adverse effects that were not even cited in those original opinions.

40. The first new claim is that "there seems now to be agreement" that oestradiol 17 β increases the risk of "endometrial adenocarcinomas", citing a single study completed by Takahashi *et al.* in 1996, well before the completion of the EC's opinions. However, like much of the other scientific evidence relied upon by the EC, the Takahashi study examined adverse effects that result from exposure to oestradiol at doses above a certain threshold. The study presents no evidence that the levels of hormones that would be expected from meat from treated animals cause these effects.

41. The second new claim is that oestrogen plays a role in the hypothesized relationship between stem cells and breast cancer, citing a recent study by Smalley and Ashworth.²⁷ However, a review of this study reveals that it did not even investigate the role of "low-dose estrogens" in tissue stem cell proliferation, but simply hypothesized a relationship between stem cells and breast cancer. Quite apart from the fact that the study failed to identify adult mammary stem cells, which it hypothesized led to breast cancer, there are many other sources of oestrogen that would affect proliferation of these stem cells far more than would dietary sources of hormones. In other words, the relevance of this study to a safety assessment of these hormones for these uses is questionable. The authors themselves indicate the hypothetical nature of their findings when they conclude that "these issues are going to keep the field of mammary stem cell biology occupied for many years to come".²⁸

42. The EC then goes on to present two additional studies, which were also not considered by the SCVPH, that it claims demonstrate a relationship between pre-pubertal growth and risk of breast cancer. The first study, by Lampit *et al.*, simply demonstrates that oestrogen replacement therapy for prepubertal children, already undergoing therapy to delay precocious puberty, resulted in changes to growth patterns. The EC attempts to combine these results with a second study, by Ahlgren *et al.*, that postulated a relationship, on the basis of epidemiological studies, between cancer and a number of other factors, one of which was prepubertal growth rates. The link that the EC is trying to draw between these two studies is, however, simply too tenuous to support the conclusion that the EC suggests.

43. Similarly, in its comments on the experts' responses to **Question 14** on whether the EC's opinions on oestradiol 17 β follow the four steps in the risk assessment set out in the Codex guidelines, the EC argues that Dr. Guttenplan failed to take into account two studies concerning the ACI rat and ERKO/Wnt mouse. That the question was not whether new scientific evidence supports the EC's claims, but whether the SCVPH opinions follow the four steps of a risk assessment seems to have been lost on the EC. The new studies referred to by the EC do nothing to undermine the "mixed rating" that Dr. Guttenplan gave the EC's opinions.

44. The EC concludes its presentation of its new claims of adverse effects by lamenting that the new material was "not at all considered by the experts". However, the new material says nothing about meat from treated animals and, more importantly, the claims of adverse effects were not considered by the SCVPH in its opinions. Since the experts' role is not to review additional material and determine whether the hormones at issue pose a risk of adverse effects, the EC does not explain how any of this material – only introduced by the EC with its comments – is relevant to the issue of whether the SCVPH opinions amount to a risk assessment that is appropriate to the circumstances. The new studies do not change what the SCVPH did or did not do in its 1999, 2000 and 2002 opinions.

²⁷ See Smalley, M. & Ashworth, A., *Stem Cells and Breast Cancer: A Field in Transit* (2003) Vol. 3 online: www.nature.com 832-844.

²⁸ *Ibid.*, at p. 843.

D. CONSUMPTION OF MEAT CONTAINING HORMONES

(a) Carcinogenicity

45. In its comments on the experts' responses to **Question 15**, the EC only explains half the story about the Appellate Body's interpretation of the term "potential". By suggesting that the Appellate Body found that a risk assessment need only identify whether adverse effects are "possible", the EC has attempted to reduce the requirements of a risk assessment to only its first step, the hazard identification.²⁹ To accept the simplistic definition of "potential" as "possible" eliminates the most important element of a risk assessment, that is, the evaluation of the potential for occurrence. In the entire context of the Appellate Body's ruling, such a narrow reading is not justified. The Panel may wish to ensure that the experts are aware of the full context of the requirements of a risk assessment under the *SPS Agreement*, as set out by the Appellate Body.

46. In its comments on the experts' responses to **Question 16**, the EC again misrepresents the Appellate Body's findings related to quantitative versus qualitative risk assessments. Contrary to the EC's claim, nowhere did the Appellate Body make a finding as far reaching as a "*qualitative* assessment of risk is acceptable for the purposes of the *SPS Agreement*". As explained above,³⁰ what the Appellate Body said was that there is no requirement for a "risk assessment to establish a minimum magnitude of risk".³¹ If the EC had identified that there was no threshold dose of hormones below which adverse effects would not occur, then it would be appropriate not to assess quantitatively the exposure. However, since the experts confirm that the EC has not demonstrated there are adverse effects that do not exhibit a threshold, the EC is required to evaluate exposure data. This requirement does not emerge from some general requirement to conduct a quantitative risk assessment, but rather from the need to evaluate the potential occurrence, even as this evaluation need not lead to the identification of a "minimum magnitude of risk".

47. In its comments on the experts' responses to **Question 17**, the EC attempts to compare the advice provided by Dr. Boisseau and Dr. Boobis to that of Dr. Lucier that was disregarded by the Appellate Body in *EC – Hormones*.³² The comparison is not appropriate. The advice that was disregarded by the Appellate Body related to Dr. Lucier's quantification of the risk of developing breast cancer from consumption of residues of hormones in meat from treated cattle as one in every million women in Canada, the United States and Europe. The Appellate Body disregarded this calculation because it was not the result of any study that supported the risk that Dr. Lucier calculated. In other words, his specific calculation of the quantum of risk was merely unsupported speculation. This is to be contrasted with the expertise and the advice of Dr. Boisseau and Dr. Boobis on the issue of the formation of catechol oestrogens in meat. These experts are not speculating a quantum of risk, but rather are providing their expert advice on basic biological processes well within their area of expertise developed over long careers of evaluating veterinary drugs and other chemical substances.

48. With respect to the EC's comments on the experts' responses to **Question 18**, Canada has already commented above³³ on the EC's claim it has provided scientific evidence that oestradiol 17 β is genotoxic *in vivo*. The EC then goes on to make the surprising and entirely unjustified claim that in any event it is Canada that must demonstrate that residues from hormones from meat from treated animals will not cause genotoxic effects. Quite apart from the fact that the EC makes no attempt to justify why Canada would bear such a burden, this assertion ignores some basic facts about this

²⁹ According to the international techniques for risk assessments, this is the "hazard identification" stage. According to the Appellate Body, this is the "identification of adverse effects on human health".

³⁰ See Canada's comments above, at para. 22.

³¹ See *EC – Hormones*, Report of the Appellate Body, at para. 186.

³² *Ibid.*, at para. 198.

³³ See Canada's Comments, Question 13.

dispute: it is the EC that claims to have found evidence that the hormones cause adverse effects; it is the EC that has adopted an SPS measure to ban these hormones as a result; and it is the EC that now claims that this measure brings it into compliance with previous findings of non-compliance. As a result, there is no question that it is now the EC that bears the burden of demonstrating that its claims are justified on the basis of scientific evidence. It has not done so, and no attempt to shift the burden to Canada alters its failure to do so.

49. In its comments on the experts' responses to **Question 19**, the EC claims that the mode of action of cancer is not relevant from a regulatory perspective. On the contrary, the mode of action is very relevant to regulators. It is also very relevant for purposes of compliance with obligations under the *SPS Agreement*, as the correct identification of the mode of action of cancer will determine whether a given SPS measure is justified by the science. If the mode of action is through hormonal activity, which clearly exhibits a threshold response, a risk assessment that ignores the existence of a threshold will not be "appropriate to the circumstances", and will not meet the requirements of the *SPS Agreement*. On the other hand, if the mode of action is through genotoxicity, regulators would be justified in eliminating exposure to the substance entirely if it were a type of genotoxic effect that did not exhibit a threshold.

50. The experts have indicated in their responses that the carcinogenic potential of these hormones is related to their hormonal activity, and also that there is no evidence of genotoxic effect *in vivo*. As a result, SPS measures (*i.e.*, the EC's bans) that are based on an assessment that as a matter of principle assumes no threshold (*i.e.*, the SCVPH opinions) can not be considered to be based on an appropriate risk assessment.

51. Furthermore, the EC's claims that there is also evidence of a relationship between exposure to oestradiol 17 β during early development and the risk of breast cancer warrant further comment. The study cited by the EC in support of this claim does not specifically identify hormones from meat from treated animals as the source of exposure³⁴ and, more importantly, it only concludes that there "may be potential" for early hormone-induced changes to the mammary glands to be "prerequisites" for tumours. The EC therefore significantly overstates the case when it concludes that it is "beyond doubt" that there is such a link. In the absence of any evidence to support this assertion, it is simply that: an unsupported assertion. In any event, the EC does not explain the relevance of hormone exposure during early development to the experts' responses to this question, which is about the relationship between genotoxicity and the ability to establish dose thresholds.

52. In its comments on the experts' responses to **Question 20**, the EC criticizes Dr. Boobis for basing his reply on "assumptions" and "hypothesis" that oestradiol 17 β is not genotoxic and that a threshold can be set. However, Dr. Boobis's advice on the genotoxic potential of oestradiol 17 β is based on far more than assumptions; it constitutes his reasoned conclusions based on his experience with the issues, his review of the scientific evidence and his expertise in the area. It is the EC that bases its SPS measure on an unproven hypothesis about genotoxicity.

53. The EC also argues that it is "no longer seriously disputed" that oestradiol 17 β is genotoxic, pointing again to the findings of JECFA on the matter. Canada has already addressed the significance of JECFA's findings of "genotoxic potential" in its own comments on the experts' responses to Question 20.³⁵ Nothing the EC has indicated in its comments changes the fact that if JECFA considered that oestradiol 17 β were genotoxic, it would not have established an ADI for it.

³⁴ In fact, as Canada has explained in its own comments on Question 39, there are many sources of oestrogen during early development, all of which would be far greater than residues of hormones from meat from treated animals. See Canada's Comments, at para. 146.

³⁵ *Ibid.*, at paras. 79-82.

54. The EC also seems to believe that the issue is whether the JECFA assessments have now become outdated simply as a result of the passage of time. On the contrary, the issue is whether the EC has identified scientific evidence that the existing assessments, and the international standards based on them, cannot achieve the EC's level of protection, which is, in fact, the same as that embodied in the international standards. The focus then should be primarily on what the EC's "new" scientific evidence says about the safety of the hormones. On this point, the experts have not indicated that this new evidence changes the JECFA assessments.

55. With respect to its comments related to **Question 21**, the EC again confuses the issues by responding to a question about the genotoxic potential of the other five hormones with reference to hormone levels in prepubertal children. This response seems to suggest that the EC believes that the genotoxic potential of these hormones is dose dependent and has a threshold below which it will not occur. By lumping together its claims that depend on doses and thresholds with claims that do not depend on doses and thresholds, the EC simply demonstrates that its arguments are internally inconsistent and contradictory.

56. In its comments on the experts' responses to **Question 22**, the EC again refers to Dr. Boobis' "assumptions" about the genotoxic potential of oestradiol 17 β , when in fact his advice is not based on assumptions, but on extensive evidence and opinion from the international scientific community that oestradiol 17 β is not genotoxic *in vivo*.

57. With respect to its comments on the issue of DNA repair mechanisms, the EC raises concerns never before raised by it or the SCVPH about an "increase in the rate of damage". It suggests that "if the rate of repair were constant", increases in the rate of damage caused from residues of hormones would lead to increases in the rate of unrepaired damage. Quite apart from the fact that it provides no scientific evidence to support the assertion that the rate of repair is constant, and apart from the fact that the experts have all said that there is considerable redundancy in the repair mechanism, even the EC acknowledges, by presenting the issue as a hypothetical, that its assertion is completely untested.

58. In its comments on the experts' responses to **Questions 23 and 24**, the EC acknowledges what it failed to acknowledge in comments on Question 13 above, that "epidemiological studies will not be able to discriminate (or separate out) the true origin of cancer because of so many co-founding factors." It is not clear, however, why the EC believes that this acknowledgment undermines Canada's position, since Canada has never argued that epidemiological studies can prove that the hormones are safe. Rather, Canada has only ever argued that the results of epidemiological studies provide no information about causal relationships between adverse effects and consumption of hormones from meat from treated animals.

59. The EC's additional comments on the IARC studies, on which it places so much emphasis in its response to Question 13, are also notable. Even though it misrepresents what those studies actually show,³⁶ it still has to acknowledge that "this is just an indication that there might be a link between consumption of red meat and breast cancer". In the end, it appears that the EC and Canada agree on the limited value of epidemiological studies in the conduct of a risk assessment appropriate to the circumstances of these substances.

³⁶ The EC's statement that the IARC studies show that the "frequency of breast cancer in countries where hormones are allowed is higher compared with countries where the hormones have not been used" is misleading. If it is referring to IARC's classification of oestrogen as a Group I carcinogen, then the data relied upon in that conclusion did not distinguish between areas where growth-promoting hormones are used and where they are not. In other studies, only a very selective reading of the data shows any cancer rate differences exist between such regions. To the extent these data show any differences at all, Dr. Boobis also cautions against "ecological fallacies" when interpreting such data.

60. In its comments on the experts' responses to **Question 25**, the EC again attempts to impugn the data on which JECFA relied for its assessment that exposure to the hormones at levels below the established ADI would not lead to adverse effects. It again tries to claim that simply because the data are "old", they are no longer valid, without providing any scientific evidence that contradicts the conclusions of JECFA based on those data. Dr. Boobis has not imposed a higher standard on the EC than was imposed on JECFA; he is simply indicating that the EC has failed to demonstrate scientifically, either in the three additional studies or in any other studies, that there is a potential for adverse effects.

61. The EC also again criticizes JECFA's level of protection of "no appreciable risk" as being subjective and qualitative. Not only is this criticism ironic in light of the EC's own defence of the appropriateness of "qualitative" risk assessments, but it is also wrong. As Canada has explained in its comments above on the EC's comments on risk assessment techniques,³⁷ "no appreciable risk" can be equally expressed as "zero observed risk". This is not 1% or 10% risk, as the EC suggests here, but is zero risk. This does not mean that there is no hypothetical risk; it simply means that no adverse effects have been observed to support a conclusion that there are risks. In other words, any risk that might be inherent in the expression "no appreciable risk" is simply a theoretical or hypothetical one.

62. In its comments on the experts' responses to **Question 26**, the EC seems to shift position once again on the value of epidemiological studies. In earlier comments, it states that epidemiological studies confirm the existence of adverse effects; in other comments, it states that epidemiological studies cannot prove one way or another that adverse effects will occur; and now it states that it relies upon the results of epidemiological studies simply to demonstrate that scientific uncertainty is growing. The only thing that seems to be uncertain is what the EC actually believes is the value of such studies in support of its claims. The EC places considerable emphasis on the statements by several experts that the results are "consistent with" an association between hormone residues in meat and cancer outcomes. However, in light of the clear advice from the experts about the inability to separate confounding factors, finding that they are "consistent with" an association says very little about demonstrable association.

(b) Residue Analysis

63. In commenting on the responses to **Question 27** concerning residues of synthetic hormones, the EC asserts that the differences in residues are "not only structural/chemical but also qualitative and quantitative." What the EC means by "qualitative" is left unclear. In terms of "quantitative" differences, the EC refers to one of the 17 studies commissioned by the European Commission conducted by Rainer Stephany and the conclusions contained therein relating to the concentration of oestradiol-17 β in meat from treated cattle.³⁸ However, concentrations of oestradiol 17 β (a natural hormone) provide no information about quantitative differences in residues of synthetic hormones, which is the focus of this question.

64. The study provides no support for the EC's suggestion that actual residue data for synthetic hormones differ from data submitted as a part of the authorization of synthetic hormones.

65. In commenting on the experts' replies to **Question 28** concerning residues of synthetic hormones, the EC attempts to discredit Dr. Boisseau's reply by asserting that "estradiol-alpha", by which the EC presumably means oestradiol-17 α (alpha), is a main residue found in the liver of cattle treated with oestradiol 17 β and that this residue gives rise to human health risks. In the next paragraph, however, the EC cites Dr. de Brabander's conclusion that residues of endogenously

³⁷ See Canada's comments above, at paras. 18-21.

³⁸ Stephany, R., *Hormones in meat: different approaches in the EU and in the USA*, (2001) 109 (Suppl. 103) APMIS S357, at p. 361 ("Stephany Study") (Exhibits EC-49, CDA-12).

produced natural hormones in cattle are in the 17 α (alpha) form (inactive), while the use of natural hormones used for growth promotion "may lead to residues in the [oestradiol 17] β form (active form)". This latter conclusion suggests that, if indeed the EC is correct that oestradiol-17 \forall (alpha) gives rise to human health risks (a bald proposition unsupported by any evidence), the risk comes from eating meat from untreated cattle. Dr. de Brabander does not suggest that meat from treated cattle contains a higher proportion of oestradiol-17 \forall (alpha). Thus the EC's argument disproves itself.

66. In commenting on the experts' replies to **Question 29** concerning residues of synthetic hormones, the EC asserts that the SCVPH considered ADIs and MRLs (Maximum Residue Limits) recommended by JECFA and "went even further and examined tolerance levels recommended by the USA." This statement is both inaccurate and misleading. For trenbolone acetate (TBA), the SCVPH did not even refer to, let alone consider, MRLs recommended by JECFA, choosing instead to compare tolerance limits set by the US Food and Drug Administration (FDA) to JECFA's ADI.³⁹ Whatever the merit of this approach, it says nothing about the appropriateness of JECFA's MRLs. Moreover, the SCVPH failed completely to address JECFA's conclusions, which are in part:

The Committee recommended MRLs for β -TBOH in muscle and α -TBOH in liver of 2 $\mu\text{g}/\text{kg}$ and 10 $\mu\text{g}/\text{kg}$ respectively....These MRLs are not likely to be exceeded with good practice in the use of veterinary drugs.

Conservative estimates using these MRLs and the daily intake values for edible tissues given in Section 2.6 indicate that the ADI for TBA of 0.02 μg per kg of body weight should not be exceeded at any time after implantation of the drug. The maximum concentrations of residues occur at 15-30 days after implantation and are below the recommended MRLs; concentrations will be even lower at the usual withdrawal time of 60 days.⁴⁰

67. Thus, even if withdrawal periods are not respected, the ADI would not be exceeded.

68. In relation to zeranol, the SCVPH simply refers to the MRLs set by JECFA⁴¹ and again compares them to the US FDA tolerances. This says nothing about whether the MRLs set by JECFA would lead to intake sufficient to exceed the ADI. Nor did the SCVPH evaluate JECFA's conclusion in its residue monograph for zeranol that "[t]he total residues [of zeranol] in liver, kidney, muscle and fat do not exceed 10, 2, .2 and .3 $\mu\text{g}/\text{kg}$, respectively, at any time post-implantation".⁴² Again, even if the withdrawal periods were not respected, the ADI would not be exceeded.

³⁹ 1999 SCVPH Opinion, at p. 57 (Exhibit CDA-2). Surprisingly, the SCVPH used temporary ADIs set by JECFA in 1987, as opposed to the final ADI set by JECFA in 1989. The final ADIs are found in JECFA, *Evaluation of certain veterinary drug residues in food: Thirty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 788 (Geneva: WHO, 1989), at p. 62 (JECFA's 34th Report) (Exhibit CDA-19).

⁴⁰ JECFA's 34th Report, at p. 42 [emphasis added] (Exhibit CDA-19). The Residue Monograph for TBA prepared for the 34th Meeting of JECFA is found at Exhibit CDA-38.

⁴¹ JECFA, *Evaluation of certain veterinary drug residues in food: Thirty-second Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 763 (Geneva: WHO, 1988), at p. 28 (Exhibit CDA-18).

⁴² JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Thirty-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food and Nutrition Paper, No. 41/1 (Rome: FAO, 1988), at p. 46 (32nd JECFA, Residue Monograph for Zeranol) [emphasis added] (Exhibit CDA-39).

69. Lastly, in relation to MGA, the SCVPH did not consider the MRLs recommended by JECFA for MGA, let alone the detailed residue monographs for this substance.⁴³ It is worth noting that while the JECFA recommendations were made after the SCVPH opinions, they were made prior to the establishment of this Panel in January 2005.

70. The foregoing demonstrates that the EC, through the SCVPH, did not consider whether actual residues of the synthetic hormones in meat from treated cattle would exceed the MRLs recommended by JECFA. It also failed to consider whether compliance with the MRLs recommended by JECFA would lead to an intake of residues in excess of the Codex ADI. Thus, in this regard, the EC has not provided a scientific justification for why established international standards would not meet its chosen level of protection.

71. In commenting on the experts' replies to **Question 30** concerning residues of natural hormones, the EC again confuses and distorts the JECFA ADI. As will be discussed below,⁴⁴ although JECFA referred to background levels of circulating hormones, their daily production and metabolic clearance rates (MCR),⁴⁵ the ADI is not based on a calculation of endogenous production of natural hormones, but on the NOAEL. Therefore, even if background levels, daily production rates and MCRs of the natural hormones in prepubertal children are lower than first thought, the ADI would not be affected.⁴⁶

72. In commenting on the experts' replies to **Question 31** concerning the variation in physiological levels of natural hormones in meat from untreated cattle, the EC again presents inaccurate information. First, the EC inaccurately states that Dr. de Brabander refers to the EC study indicating that consumption of meat from treated cattle contains 7.5 times more oestrogens than meat from untreated cattle. Presumably, the EC is referring to the Stephany Study, cited earlier in relation to Question 27. However, Dr. de Brabander never once refers to this study, nor does he provide any quantitative estimate of the amount by which natural hormones in meat from treated cattle vary from meat from untreated cattle. Second, on a more substantive level, the EC inappropriately cites the average level of oestradiol 17 β as opposed to the more appropriate median value, used by the author of the study. The author writes:

From *ad random* studies in 1998 and 1999 with meat imported from the USA to the EU or obtained from the US domestic market (25-26) it is estimated that the median dietary intake of 17 β -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. This has to be compared with the recently found median dietary intake of 17 β -estradiol of 6.5 nanogram via a 50 gram hens egg....From this comparison the

⁴³ JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Fifty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/14 (Rome: FAO, 2002) (58th JECFA, Residue Monograph for MGA) (JECFA's 58th Report) (Exhibit CDA-35); and JECFA, *Residues of some veterinary drugs in animals and foods: Monographs prepared by the Sixty-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives*, FAO Food And Nutrition Paper, No. 41/16 (Rome: FAO, 2004) (62nd JECFA, Residue Monograph for MGA) (Exhibit CDA-33).

⁴⁴ See Canada's comments below, at paras. 84-87.

⁴⁵ JECFA, *Toxicological evaluation of certain veterinary drug residues in food: prepared by the Fifty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Food Additives Series No. 43 (Geneva: WHO, 2000) (Toxicological Monographs for Oestradiol-17 β , Progesterone and Testosterone), at pp. 51, 82 and 90 for each hormone, respectively (Exhibit CDA-11).

⁴⁶ The EC's comments on misuse and abuse will be addressed later in these comments in the Section on GVP.

preliminary conclusion is that hens eggs are a major source of 17β (and 17α -estradiol) in the daily "normal" diet.⁴⁷

73. Thus, residues of natural hormones in meat from treated cattle are only twice the median level found in meat from untreated cattle. Moreover, total residues of all oestradiol 17β in 250 grams of beef (approximately $\frac{1}{2}$ lb) from treated cattle (5 ng) are less than that found in one egg (6.5 ng)! Not unexpectedly, the EC ignores this finding and the main recommendation of the Stephany Study that "[t]he 'hormones in meat problem' should be evaluated in relation to all facts about the actual total dietary intake of 'hormones', e.g. from meat(products), poultry, milk, dairy products, eggs, and fish(products) taking also into account the effects of various ways of food production and of 'household' cooking".⁴⁸

74. The above results and conclusions are consistent with those of the UK Sub-Group of the Veterinary Products Committee, which reviewed data relating to the natural occurrence of steroid hormones in a variety of food sources.⁴⁹ Those data included a study by Sonja Hartmann, *et al.*, which concluded:

Meat does not play a dominant role in the daily intake of steroid hormones...The main source of estrogens and progesterone are milk products (60-80%). Eggs and vegetable food contribute in the same order of magnitude to the hormone supply as meat does.⁵⁰

75. The Stephany and Hartmann studies support Canada's basic point that the risks associated with hormones for growth-promotion purposes cannot be appropriately evaluated without considering exposure to other sources of dietary hormones. The data also suggest that the EC's stated high level of protection for its citizenry, particularly prepubertal children, is more rhetoric than reality. One need only consider that few prepubertal children consume anything close to 250 grams ($\frac{1}{2}$ lb) of beef on a daily basis, while milk products and eggs are staples of a child's diet, to see that such claims ring hollow. Given the significance of other dietary sources of hormones in comparison with the trivial contribution from the use of growth promotants, the EC's purported concerns about genotoxicity and endocrine disruption, amongst others, begin to look less and less genuine.

76. In commenting on the replies to **Question 32** concerning unvalidated detection methods, the EC criticizes Dr. Boisseau's advice as being "scientifically unsound." However, it is clear from Dr. Boisseau's reply that he is referring to the use of detection methods for determining compliance with MRLs. In that context, his statement that detection methods need only be sensitive enough to detect residues in excess of MRLs is scientifically accurate. To the extent that the "ultra-sensitive" detection methods referred to by the EC are intended to evaluate levels of naturally occurring hormones in a variety of food sources,⁵¹ it should be recalled that data on these levels currently exist and are before this Panel.⁵² Unless and until new, more sensitive detection methods are developed and

⁴⁷ Stephany Study, at p. 361 (Exhibits EC-49, CDA-12).

⁴⁸ *Ibid.*

⁴⁹ UK, Sub-Group of the Veterinary Products Committee, *Executive summary and critical evaluation of the scientific reasoning and methods of argument adopted in the opinion of the Scientific Committee on Veterinary Measures Relating to Public Health which assessed the potential risks to human health from hormone residues in bovine meat and meat products*, October 1999, at pp. 11-12 (Exhibit CDA-6).

⁵⁰ Hartmann, S., *et al.*, *Natural occurrence of steroid hormones in food*, (1998) 62:1 Food Chemistry, at p. 18 ("Hartmann study") (Exhibit CDA-50).

⁵¹ It is unclear to what use the "ultra-sensitive" detection methods are to be put. However, one could infer from the introduction to Section 4.1 in the 2002 SCVPH Opinion that the intended use is to determine with greater precision the levels of naturally occurring endogenous hormones in the entire food basket.

⁵² See UK Sub-Group Report (Exhibit CDA-6); and Hartmann study (Exhibit CDA-50).

validated that call into question the accuracy of the current data, the current data should be accepted as accurate.

77. In commenting on the experts' replies to **Question 33**, the EC implies that JECFA is keeping from the Panel and the public the residue data it relied upon during its 1999 review, thereby preventing an "open and objective" verification. One need only review the 50-odd pages of residue data summarized in the residue monograph prepared for JECFA's 52nd Meeting (summarized by Dr. Arnold from the German Federal Institute of Health, no less!) to appreciate the exaggerated and sensationalist nature of the EC's claim in this regard.⁵³

78. In relation to the EC's comments on the experts' replies to **Question 35** concerning MGA and whether "subsequent reports of JECFA, prior or subsequent to the adoption of the EC Directive, also relied on the same studies", it is important to recall that the MRLs recommended by JECFA in 2000 were only "temporary" pending the "receipt of information on an analytical method suitable for quantifying residues of melengestrol acetate in liver and fat tissue. This information is required for evaluation in 2002".⁵⁴ Indeed, as explained by Canada in its comments on the experts' answers (Question 29), a validated detection method was submitted and accepted by JECFA during its 58th meeting in 2002.⁵⁵ Contrary to the EC's view, these data are hardly "old" and "outdated".

(c) Dose-Response Relationship

79. In its comments on the experts' responses to **Question 36**, the EC again misrepresents the Appellate Body findings related to "quantitative" analysis, which Canada has already addressed in its comments above.⁵⁶

80. With respect to its further claim in its comments on that question that Dr. Boobis acknowledged that no dose-response assessment may be required, it is important to note that Dr. Boobis only accepted that to be the case if two conditions were present: 1) the particular mode of action for the genotoxic effect is of a kind that does not exhibit a threshold response; and 2) it is confirmed in *in vivo* tests.⁵⁷ As Dr. Boobis advised, neither of these conditions has been met in the case of these hormones when used as growth promoters.

81. The EC then cites the absence of "internationally agreed principles" on when to conduct a dose-response assessment to justify its failure to have conducted one. However, the real issue is not whether the EC is required to do so under international risk assessment techniques but, rather, whether it is appropriate in these circumstances to fail to conduct a dose-response assessment in the course of a risk assessment. As Canada has argued elsewhere,⁵⁸ it is not possible appropriately to evaluate the potential occurrence of adverse effects from residues of hormones from treated meat without first knowing the dose at which such adverse effects will not occur.

82. With respect to the EC's comments on the experts' responses to **Question 37** concerning whether a dose response assessment is necessary, it is sufficient to note that contrary to the EC's claim Dr. Boobis and Dr. Boisseau do not agree with the EC, but rather they agree with Canada's statement.

⁵³ JECFA, *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper No. 41/12 (Rome: FAO, 2000), at 37-90, and 137-140 (Exhibit CDA-17).

⁵⁴ JECFA, *Evaluation of certain veterinary drug residues in food: Fifty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series 900 (Geneva: WHO, 2001) (54th JECFA, Technical Report for MGA), at pp. 79-80 (Exhibit CDA-36).

⁵⁵ See Canada's Comments, at para. 111. Also see JECFA's 58th Report, Residue Monograph for MGA, at pp. 56-59 (Exhibit CDA-35).

⁵⁶ See Canada's comments above, at para. 22.

⁵⁷ See Canada's Comments, Question 36.

⁵⁸ See Canada Rebuttal Submission, at paras. 80-82.

To the extent that they describe any circumstances in which the statement would not be true, such as when genotoxicity is confirmed *in vivo*, those circumstances do not apply here. In fact, they clearly indicate that a dose-response assessment is critical to establishing an ADI and MRL.

(d) Sensitive Populations

83. In commenting on the experts' responses to several questions under this section, the EC makes a number of claims that reflect a misunderstanding of the relationship between the establishment of ADIs and the identification of background levels⁵⁹ and that rely too much on a single unvalidated measurement methodology (*i.e.*, the Klein recombinant cell bioassay (RCBA)⁶⁰).

84. The EC claims in its comments on the experts' responses to **Question 38** that JECFA cannot set ADIs and MRLs without accurate data on background levels. However, nowhere – at least, nowhere that Canada can find and the EC has not provided a source – is it indicated that JECFA considers data on background levels to be "essential for determining the ADI". On the contrary, the establishment of an ADI, and hence an MRL, does not depend at all on the identification of background levels. Rather, it depends on actual observations of adverse effects at given dose levels, to which appropriate safety factors are applied to protect against variation in sensitivity between different human populations.

85. The general intention behind linking background levels with the establishment of ADIs for these hormones – which the EC does in almost all its comments in this section – is to create confusion between two distinct approaches to measuring exposure. On the one hand, there is the JECFA approach of identifying a NOAEL, applying safety factors and establishing an ADI, none of which depends on the identification of background levels. On the other hand, there is the EC's attempt to compare the proportion of intake exposure (which, incidentally, it never actually estimates) to background levels, and assert that if background levels are lower than once thought, the risk must therefore be higher simply because the ratio of intake (exogenous) dose to background (endogenous) levels would be higher.

86. At no point, however, does the EC explain this relationship. Even if the EC demonstrates background levels are lower (which it has not), since JECFA's ADI approach is based on actual observed adverse effects regardless of the background level, a change in background levels is not relevant to whether adverse effects have been observed and therefore is not relevant to the ADI.

87. To place this issue in a slightly different context, if no evidence exists that consuming an egg (which has 6ng of oestradiol 17 β , an amount equivalent to that in 250 grams of beef from treated cattle) has adverse effects on the endocrine systems of prepubertal children, then studies using genetically modified yeast that suggest that the background levels of endogenous hormones in prepubertal children are lower than first thought, do not demonstrate that consuming an egg now has greater risk.

88. The experts in their responses to **Question 41** have of course confirmed that populations with lower background levels are at greatest risk of adverse effects from exposure to hormones, and they have also confirmed that this is so because the proportion of exogenous hormone levels to endogenous exposure would be greater. However, this statement of basic physiology does not in itself confirm that even if it turns out that background levels are lower than once thought, the appreciation of the risk

⁵⁹ Canada understands that for the general purposes of the review of the scientific and technical material, the term "background levels" can be used interchangeably with "circulating levels" "endogenous levels" and "physiological levels".

⁶⁰ Klein K.O., *et al.*, *Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay* (1994) 94 J Clin Invest 2475–2480 (Klein RCBA).

would be greater. New test results that suggest background levels are lower than once thought simply change the understanding of the levels themselves, and not the risks of adverse effects.

89. In other words, for the purposes of establishing the ADI, the ratio that matters is not that between hormone intake and background hormone levels, but rather that between the background hormone levels of the populations used to identify the NOAEL and other subpopulations. And as the experts indicate in their answers to **Question 42**, JECFA already takes into account the expected lower background levels in sensitive populations.

90. In its comments on the experts' responses to **Questions 38, 39 and 40**, the EC makes several confusing and unfounded assertions about the validity and importance of background level data generated by the Klein RCBA. First, in its comments on **Question 38**, it discounts the importance of validation of scientific methodologies in support of scientific conclusions, claiming that the ultrasensitive Klein RCBA need not be validated at all for the results to have any importance. There is no basis for such a claim. It requires more than one unvalidated attempt to generate competing data to cast doubt on the data generated by radioimmuno assays (RIA). The claim that JECFA uses data from assays that have not been validated is also unfounded. JECFA goes to great lengths to validate the quality and precision of the data on which its recommendations are based. The EC did nothing to validate the data generated by the Klein RCBA.

91. In its own comments on the experts' responses to **Question 39**, the EC seems to indicate that it does not even believe the Klein RCBA is valid, when it contradicts the comments it made on **Questions 38 and 40**. In its comments on these latter questions, the EC claims that the Paris assay results overestimate the levels compared to the Klein RCBA results. But in its comments on the question coming between these two, it supports Dr. Sippell's attempt to validate the Klein RCBA results with reference to a "number of sources confirming the values" generated by Klein. It seems to have been lost on the EC that the only "confirming" source offered by Dr. Sippell was that of the Paris assay. So, whereas the EC does not consider the Paris assay results to be credible enough to be used to demonstrate that Klein is inaccurate (as suggested by Dr. Boobis), the EC does believe that these results are credible enough for purposes of confirming that Klein is accurate (as suggested by Dr. Sippell).

92. In the end, the EC itself dispels any doubt about whether it is convinced of the validity of new methodologies for measuring background levels, or the legitimacy of the data these have produced. It sums up its concerns in its comments on both **Questions 38 and 40** when it notes that the "real values for serum 17 β -oestradiol in prepubertal children still remain to be properly documented". In light of the uncertainty about the validity of the new measurements and the continued legitimacy of JECFA's ADI approach – which does not depend on these measurements – the EC has not demonstrated that JECFA's recommendations need to be modified.

(e) Bioavailability

93. In its comments on the experts' responses to the only question of this section (**Question 43**), the EC makes the same mistake as it makes under the section on sensitive populations when it suggests that new information on bioavailability calls into question the validity of the JECFA-established ADIs. As Canada has already explained in its own comments on the experts' responses to the questions,⁶¹ the actual amount of hormones that is bioavailable does not affect the validity of the ADI. Rather, the ADI is based on observed adverse effects from a given oral dose, which means that the ADI represents, in the words of Dr. Boobis, a "bioavailability adjusted" dose. The EC makes no comment on this concept. Instead, just as it does with the questionable re-evaluation of background levels, it also exaggerates the importance of what it considers "credible evidence" that the

⁶¹ See Canada's Comments, at paras. 162-163.

bioavailability of hormones might be higher than once thought. Neither issue, in the end, demonstrates that the international standards would not meet the EC's chosen level of protection.

(f) Good Veterinary Practice (GVP)

94. In the *EC – Hormones* dispute, the Appellate Body found that the EC did not submit a risk assessment "demonstrating and evaluating the existence and level of risk arising...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".⁶² Thus, one of the central issues in this dispute is whether, this time around, the EC has actually evaluated the potential adverse effects on human health related to the failure to comply with good practice in the use of veterinary drugs (GVP). As explained by Canada elsewhere, the EC has not done so.⁶³

95. In its comments on experts' responses to questions in this section (**Questions 44-51**), the EC challenges the unequivocal conclusion of the experts that the SCVPH made "no attempt to evaluate the risks from the resultant exposures [from] misuse or abuse".⁶⁴ The EC claims that it indeed conducted a proper assessment of these risks, citing several exhibits to support its claim, the most important of which is the European Commission's *Draft Report on the Assessment of Risks of hormonal growth promoters in cattle with respect to risks arising from abusive use and difficulties of control*.⁶⁵ However, a close review of these exhibits reveals that the EC claim is profoundly flawed.

96. It is important to clarify up front a few issues concerning GVP generally raised by the EC. First, with respect to **Question 46**, the EC's attempt to discredit JECFA's assessments of these hormones on the basis that JECFA did not assess potential misuse/ abuse is unsound. As explained by Dr. Boisseau, in recommending MRLs, JECFA assumes that GVP will be followed; for practical purposes JECFA does not examine potential compliance or control issues. While the failure to follow GVP may lead to residues that exceed the recommended MRL, and to a corresponding intake of residues in excess of the established ADI, such a failure does not undermine the validity of the MRL.⁶⁶

97. Second, in relation to **Question 48**, the EC's attempt to discredit Dr. Boobis's opinion by suggesting that he does not appreciate the distinction between "probability" and "possibility" as laid down by the Appellate Body is equally flawed.⁶⁷ The Appellate Body concluded that it is insufficient merely to identify the possibility of misuse/abuse, which is in effect all the EC did during the first *EC – Hormones* panel.⁶⁸ In correctly finding that the EC's assessment of this issue did not meet the requirements of a risk assessment consistent with Articles 5.1 and 5.2 of the *SPS Agreement*, the Appellate Body implies that a if WTO Member alleges risks to human health from failure to comply with GVP, that Member must evaluate the existence and level of risk arising from the abusive use of such a substance, not simply identify the possibility that such abusive use may occur.

⁶² *EC – Hormones*, Report of the Appellate Body, at para. 207.

⁶³ Canada Rebuttal Submission, at paras. 107-111.

⁶⁴ Response by Dr. Boobis to Question 48, at p. 42.

⁶⁵ European Commission, *Assessment of Risks of hormonal growth promoters in cattle with respect to risks arising from abusive use and difficulties of control*, Draft Report by special working group of external private experts and European Commission officials, Brussels, 29 April 1999 (Commission Draft Report on Assessment of Risks of Abusive Use) (Exhibit EC-73). This document was exhibited for the first time in the EC Rebuttal Submission, despite the Panel's specific request to the EC to identify the documents that encompass the risk assessment for its permanent ban. See Questions from the Panel after the First Substantive Meeting, 3 October 2005, Question 16.

⁶⁶ See Canada's Comments, Question 46.

⁶⁷ See EC Comments, Question 48, at p. 40.

⁶⁸ *EC – Hormones*, Report of the Appellate Body, at paras. 206-208.

98. Third, compliance with GVP is not an end in itself, but only a means for estimating whether actual residues in meat from treated cattle exceed recommended MLRs and/or lead to intake in excess of established ADIs. The EC devotes considerable effort to the question of whether Canada and the United States can demonstrate to the satisfaction of the EC that compliance with GVP has been assured in their respective territories, while practically ignoring the more fundamental question of whether actual residues in Canadian meat from treated cattle exceed recommended MLRs and/or lead to intakes in excess of established ADIs.

99. On a more substantive level, the EC's purported assessment of the misuse/abuse of hormones in Canada and the United States is based on a number of assumptions about both the occurrence of misuse/abuse and the risks to human health in the unlikely event that such misuse/abuse occurs. In terms of the former, the EC assumes that because there are economic incentives to using hormones for growth-promotion purposes (increased weight gain, greater feed efficiency, *etc.*), farmers will invariably misuse/abuse them in the absence of control measures as stringent as those applied in the EC. These assumptions may be based in part on the unfortunate fact that Europe has faced a "continuous series of residue scandals with illegal 'anabolic hormones' in cattle".⁶⁹ However, without concrete evidence, extrapolating illegal conduct in one's own jurisdiction to illegal conduct in another is unjustified.

100. The notion that economic incentives will invariably lead to misuse/abuse does not reflect realistic conditions of use. It presupposes that farmers are irresponsible, concerned only about profit, and insensitive to issues of animal welfare and human health. Moreover, it assumes that weight gain is proportional to the amount of hormone administered (*i.e.*, increasing the number of implants increases weight gain and the corresponding economic benefit). This assumption is not valid. It also ignores the possibility that misuse/abuse can lead to performance below optimum levels, negative effects on future reproductive performance and side effects such as vaginal and rectal prolapses. All of this demonstrates that the simplistic notion that "economic incentives" lead to misuse/abuse does not reflect realistic conditions of use.

101. Similarly, the absence of control measures as stringent as those found in Europe does not imply that misuse/abuse is more likely. Control measures are typically proportional to the magnitude of the problem. There is simply no evidence that misuse/abuse of hormones in Canada is a problem sufficient to warrant the control measures that the EC appears to deem necessary.

102. With those comments in mind, Canada will now turn to a detailed review of the assessment report contained in Exhibit EC-73. The EC asserts that higher risk flows from misuse/abuse of hormones in several ways: (a) misplaced implants, (b) off-label uses, (c) simultaneous multiple implants, and (d) black-market drugs.

103. In terms of misplaced implants, the EC postulates that tissue from the site of application containing excessive concentrations of hormones may find its way into the human food chain. The EC then presents in Table 4 of Exhibit EC-73 hypothetical exposure scenarios for various elevated concentrations of hormones and concludes that there is a risk to human health from misplaced implants.⁷⁰ This risk can occur either because the ear into which the implant has been subcutaneously inserted may not be discarded or because implants may be incorrectly inserted in edible tissues, such as the neck muscle, shoulder or hind leg. In support of this concern, the EC cites one example from Canada that found residues in muscle tissue that could only be explained by improper placement of an implant or the application of unapproved intramuscular injections of liquid hormone preparations.⁷¹ This anomalous result hardly constitutes compelling evidence of the frequency of misplaced implants.

⁶⁹ Stephany Study, at p. 358 (Exhibits EC-49, CDA-12).

⁷⁰ Commission Draft Report on Assessment of Risks of Abusive Use, at p. 15 (Exhibit EC-73).

⁷¹ *Ibid.*, at para. 16.

Other than this one example, there is no evidence that in Canada ears with implants are processed into food or that implants are inserted into other edible parts of the cow. The EC has merely identified a possibility, unsupported by any analysis of frequency of occurrence or assessment of the impact on human health in the unlikely event that such a possibility materializes.

104. Canada notes that the risk of excessive concentrations of hormones entering the food chain is far greater when liquid hormone preparations are injected into the muscle of the animal (intramuscular injection). However, this is far more likely a problem in countries that ban outright the use of growth promotants than in North America, where subcutaneous implants in the pinna of the ear of cattle (middle third of the back-side of the ear) are permitted. In order to avoid detection, it is reasonable to assume that European farmers using illegal anabolic steroids would likely use intramuscular injections rather than pinna implants, as the latter can remain *in situ* for up to 120 days and are easier to detect.⁷² Thus, the more realistic exposure scenario for the calculations presented in Table 4 of Exhibit EC-73 is excessive exposure from residues in edible tissues (muscle and fat) resulting from intramuscular injections, a practice far more likely in Europe than in Canada.

105. In terms of off-label uses, the EC cites the presence of TBA and zeranol in veal calves (calves less than 45 days of age). This implies that some growth promotants may have been used earlier than recommended, but says nothing about the potential misuse of growth-promoting hormones later in the life of cattle.

106. In terms of simultaneous multiple implants, the EC simply fails to present any evidence relating to the frequency of inappropriate multiple dosing in practice in Canada, a fact highlighted by Dr. Boobis.⁷³ Moreover, the EC's own studies confirm that, with most applications, even at doses 10 times the recommended level, residues remain below recommended MRLs,⁷⁴ a finding also noted by Dr. Boobis. Thus, even in the unlikely event of inappropriate multiple dosing, the EC's own evidence suggests that residues, for the most part, would remain below safe thresholds.

107. Lastly, in terms of black-market drugs, the EC speculates that the economic incentives for using growth-promoting hormones "cannot exclude the emergence of a black market for less expensive or more effective substances".⁷⁵ The EC presents no evidence of illegal use of black-market drugs for growth-promotion purposes in cattle in Canada. Although the EC's own studies reveal that "[i]n the EU dozens of illegal hormones are used",⁷⁶ it is not logical to extrapolate the apparent problem with illegal hormone use in countries that outright ban all growth promotants to the North American context where growth promotants are permitted under specific circumstances. Indeed, the very availability of legal growth promotants in North America suggests that the likelihood of the misuse of illegal drugs would be much lower in Canada than in countries that prohibit outright any growth promotants.

108. In conclusion, the EC's claim that it has properly evaluated the potential for adverse effects from the misuse/abuse, a claim contradicted by the experts, does not withstand scrutiny. In addition to being based on several flawed assumptions that do not reflect realistic conditions of use, the assessment simply fails to evaluate the frequency of occurrence of misuse/abuse and the potential

⁷² In the Stephany Study, the author suggests that in the EU the mode of application of growth promotants is intramuscular injection (Exhibits EC-49, CDA-12).

⁷³ Dr. Boobis's reply to Panel Question 62, at pp. 50-51.

⁷⁴ Lange, I., *et al.*, *Hormone contents in peripheral tissues after correct and off-label use of growth promoting hormones in cattle: Effect of the implant preparations Finaplix-H®, Ralgro®, Synovex-H® and Synovex Plus®* (2001) 109 APMIS 53-65, at pp. 382-383 (Exhibit EC-17).

⁷⁵ Commission Draft Report on Assessment of Risks of Abusive Use, at para. 47 (Exhibit EC-73).

⁷⁶ Stephany, R., *Hormones found in Meat Samples from Regular Controls in the European Union and from US Imports* (2000) Chemical Awareness: Issue 9, at p. 1 (Exhibit EC-19). Also see the Stephany Study, at p. 358 (Exhibits EC-49, CDA-12).

impact on human health in the unlikely event that misuse occurs. It does not satisfy the requirements for a risk assessment under Article 5.1 and 5.2 as set down by the Appellate Body in the previous Hormones dispute.

(g) Other

109. The EC, in its comments on the experts' responses to **Question 52**, again erroneously characterizes the advice of Dr. Boobis and Dr. Boisseau as based on "assumptions and conservative interpretation", and further that these experts hold the EC's opinion to a higher standard than that to which companies were held when they first received approval for the sale of the hormones as growth promoters.

110. First, the advice from Dr. Boobis and Dr. Boisseau is based on far more than assumptions; it is based on their qualified expertise in their own areas of specialization. The EC may disagree with their advice, but that in itself does not mean it is based on assumptions. If any party in this dispute is making assertions unsupported by the scientific evidence, it is the EC itself, such as with its genotoxicity hypothesis and its reliance on unvalidated measurement methodologies.

111. Second, the EC's accusation that Dr. Boisseau and Dr. Boobis are applying a double standard ignores the history of the evaluation of the safety of these substances. Quite apart from the standard of review to which the original applicants for approval of the hormones were held, the fact remains that the hormones have been repeatedly reviewed and approved by national authorities and international standards bodies, such as Codex and JECFA, on several occasions since the original approval. None of these subsequent reviews, all of which use the latest methodologies and scientific evidence, found that there was any evidence of adverse effects. On the other hand, it is the EC that now claims to have demonstrated that there are adverse effects. It is not only reasonable but legally necessary for the EC to demonstrate, with more than hypothesis and unvalidated methodologies, the potential for the purported adverse effects to occur. Far from being a double standard, this is simply holding the EC to the same standard.

112. The EC also places considerable emphasis on a single statement by Dr. Boobis that the risks from consuming residues in meat from treated animals are "minimal". However, the EC conveniently ignores almost the entirety of the preceding paragraphs in Dr. Boobis's response, in which he states, *inter alia*, that: "none of [the] information provided by the EC demonstrates the potential for adverse effects in humans"; "[t]he studies on genotoxicity provide no convincing evidence of potential for harm in consumers"; "there would be no risk of ... [adverse] effects from ... exposures" from meat from treated cattle; and "there is no evidence that low level exposure is causing harmful effects in humans" [emphasis added]. Therefore, in light of Dr. Boobis's responses above to the issue of whether the EC has demonstrated the potential for adverse effects, it is quite clear what Dr. Boobis means when he uses the word "minimal".

113. The EC further endorses the responses of Dr. Guttenplan in a manner that is not supported by the advice of the other experts and the comments by the EC itself. The EC cites Dr. Guttenplan's support of the data generated by the Klein RCBA, despite the obvious concerns expressed about these data from all the other experts.⁷⁷ The EC then endorses Dr. Guttenplan's favourable reference to the Paris assay data to validate the Klein RCBA data, even though it stated that the former methodology was not appropriate to validate the latter methodology.⁷⁸ Finally, the EC cites these statements favourably without acknowledging that Dr. Guttenplan was simply saying that "more accurate methods of analysis could now be used" [emphasis added] to corroborate the EC's concerns, not that in fact they had been used or that the EC's concerns had been corroborated using these methods.

⁷⁷ See Canada's comments above, at paras. 89-92.

⁷⁸ See EC Comments, Question 38.

114. In its comments on the experts' responses to **Question 53**, it is sufficient to note that in quoting generously the response of Dr. Guttenplan, the EC tellingly failed to address the statement by him that "by far, estrogen is the major agent of risk and, because the concentrations of all the hormones in beef are so low, that they would be unlikely to affect the potency of estrogen". Dr. Boisseau made a very similar statement, which was also tellingly ignored by the EC.

115. The EC's comments on the experts' responses to **Question 54** are confusing and misleading. First, immediately after quoting Dr. Boisseau that the ADI represents the quantity of these residues that can be ingested daily "without causing any problem of health" [emphasis added], the EC concludes that his reply meant that "there is no doubt ... that there is a risk", without explaining how the former idea supports the latter conclusion.

116. The EC then misrepresents Dr. Boobis's answer in the same manner when it interprets his statement that the "Codex standard [of no appreciable risk] is equivalent to the EC's stated objective of 'no risk from exposure to unnecessary additional residues...'" to mean that "Codex's standard recognises that there is an [*sic*] scientifically identified risk but recommends its members to follow it...". The EC again leaves unexplained how it justifies going from the former idea to the latter. Indeed, as Canada has explained above,⁷⁹ the concept of "no appreciable risk" does not mean that JECFA/Codex have identified some risk, even if minimal; rather, it means that any risk that might exist is purely hypothetical (*i.e.*, not observable). And as the Appellate Body made clear, a risk assessment cannot be based on hypothetical risk.⁸⁰

117. In its comments on the experts' responses to **Question 55**, the EC disagrees with what the experts have to say, so it simply tries to change the subject. Instead of addressing the unanimous advice from the experts that the EC opinions did not evaluate additive risks, the EC chooses to attack the integrity of the experts and the legitimacy of their opinions, and then diverts attention to whether JECFA conducted an evaluation of such risks. The attack on the experts is unjustified: first, because they were asked whether the EC had conducted such an assessment and not whether JECFA did; and second, since it is the EC that claims that there are additive risks, it is up to the EC to demonstrate that such risks exist. In any event, the experts did indicate that JECFA had evaluated additive risks and there were no concerns about such risks arising from meat from treated animals given the extremely low doses of exposure from this source.

118. The EC then acknowledges that the SCVPH did not address additive risks "because the state of scientific knowledge available by then ... did not allow such an assessment to be completed". Given that the EC's justification for its bans relates to concerns about proven additive risks, it is nothing short of a remarkable admission that additive risks were not even assessed.

119. The EC provides contradictory comments on the experts' responses to **Question 56**.⁸¹ First, it provides that it has "clearly been shown that the effects from exposure to different estrogens are additive". Then it indicates that it "has tried to do such an assessment [of the additive risks] when the information available was sufficient, but could not complete it because of gaps in our scientific knowledge". Whichever it is, both of these statements are remarkable in light of the importance to the EC's justification of its bans of an assessment of additive risks. And to the extent that the studies cited by the EC say anything about additive risks from oestrogens, they still do not answer the question of whether hormones from meat from treated animals contribute to such additive risks.

⁷⁹ See Canada's comments above, at paras. 18-21.

⁸⁰ *EC – Hormones*, Report of the Appellate Body, at paras. 199-200.

⁸¹ It is also necessary to note the irony in the EC's criticism of the experts for failing to provide precise references in its answers.

120. In its comments on the experts' responses to **Question 57**, the EC completely ignores the advice of two of the three experts that cast serious doubt on the EC's justification of its authorization of the hormones for therapeutic and zootechnical purposes. In declaring this question unnecessary and irrelevant by virtue of certain Appellate Body findings, the EC completely misses the nature of the experts' criticism of the EC use for these purposes. The issue is not whether there was a violation for authorizing these uses, but that the mere authorization itself undermines the EC's dramatic claims that no threshold for adverse effects from these hormones can be established. This is what leads Dr. Boisseau to call it a "problem of principle" and Dr. Boobis to indicate that this demonstrates the EC believes there is in fact a threshold response. Moreover, the claim that the use of oestradiol for "such purposes is now virtually terminated" does nothing to respond to the criticisms.

121. Since the EC's comments on the experts' responses to **Question 58** merely demonstrate the degree to which its arguments rest on hypothetical situations and assumptions, nothing in its statements warrants further comment from Canada.

122. In commenting on the experts' responses to **Question 59** concerning the EC's non-existent evaluation of the potential for adverse effects on the immune system from residues of hormones consumed in meat from treated animals, the EC employs two diversionary tactics. The first is to indicate that the existing international recommendations that these substances are safe are based on "outdated" data, not on the basis that the data have been superseded, but simply on the basis that they are "old". This line of argument ignores both the fact that the age of the data does not determine their currency and, further, that in any event the hormones have been repeatedly re-evaluated by JECFA as new information becomes available, and the recommendations have remained largely unchanged. The second tactic of course is to argue that it is not the EC that must demonstrate that these adverse effects will occur, but, rather, that it is Canada that must demonstrate that they will not occur. For reasons already discussed on many occasions, this claim is without merit.

123. In its comments on the experts' responses to **Question 60**, the EC comments at great length about the bioavailability of MGA as a feed additive and on the potency of consuming implants of the other five hormones that have not been removed, but in the end provides very little by way of relevant commentary on whether one route of administration leads to adverse effects that are any different from the other route. The EC goes on to challenge Dr. Boobis's comments about the risks from misuse and abuse of MGA implants. However, the EC seems to have understood him to be advising on the implanting of MGA, which is not an approved use, even though it was clear that he was referring to only those hormones that could be administered with implants. To the extent that the EC misunderstood Dr. Boobis's comments, its own comments are of little value.

124. In commenting on the experts' responses to **Question 61** concerning the sufficiency of the evidence to conduct a risk assessment of the other five hormones, the EC does little more than continue its direct attack on the objectivity and professionalism of Dr. Boobis and Dr. Boisseau. The participation in this process of experts that have extensive experience with the evaluations of JECFA of these substances only enhances the Panel's ability to understand the considerable scientific evidence related to the safety of these hormones. Far from lacking objectivity, these experts are best placed to advise the Panel on the sufficiency of the evidence to conduct a risk assessment according to the internationally agreed techniques employed by JECFA. In this case, they both indicated the evidence was sufficient to do so.

125. In commenting on the experts' responses to **Question 62**, the EC continues again its attack, this time singling out the comprehensive and informed review by Dr. Boobis of all of the new material provided by the EC. While the EC indicates that a "more careful examination by a real expert of the same body of evidence" led to the opposite conclusions to those offered by Dr. Boobis, it neglects to inform the Panel and Canada who this "real expert" is and why his or her anonymous views should be considered more authoritative than those offered by the expert specifically chosen for

the task. In any event, it is difficult to see how the EC could consider Dr. Guttenplan's one paragraph enumeration of gaps a "more considered and objective view" than the 11 pages of analysis offered by Dr. Boobis.

III. COMMENTS ON THE COMMENTS FROM THE EC ON THE RESPONSES FROM THE INTERNATIONAL BODIES

126. In relation to the EC's comments on the responses by the international bodies to **Questions 1, 5, 16, 17, 18 and 19**, Canada will not comment at this time.

127. In relation to the EC's comments on **Questions 3 and 4**, Canada refers to paragraphs 12-14 of this document.

128. In relation to **Question 7**, Canada refers to paragraphs 23, 35-44, and 83-92 of this document.

129. In relation to **Question 8**, Canada refers to paragraphs 35-44 of this document.

130. In relation to **Question 9**, Canada refers to paragraphs 18-21 of this document.

131. In relation to **Question 10**, Canada refers to paragraphs 12-14, 83-92, 116-118 of this document.

132. In relation to **Question 11**, Canada refers to paragraph 77 of this document.

133. In relation to **Question 12**, Canada refers to paragraphs 16 and 17, 18-21 of this document.

134. In relation to **Question 13**, Canada refers to paragraph 77 of this document.

135. In relation to **Question 14**, Canada refers to paragraph 5 of this document.

136. In its comments on the responses **Question 15**, the EC continues to ignore the existence of the *Recommended International Code of Practice for Control of the Use of Veterinary Drugs*, of Codex, which was mentioned by Codex as well as Dr. de Brabander.

137. In relation to **Question 20**, despite the explanation by JECFA that the three natural hormones had been placed on the agenda of JECFA in 1999 at the initiative of the JECFA Secretariat to ensure that all the latest information had been evaluated, the EC insists that, in its words, "most of the data were the same old data". The Panel may wish to ask JECFA for further clarification in this regard. Canada also refers to paragraph 77 of this document.

138. In relation to **Questions 23, 24, 25 and 26**, Canada refers to paragraphs 29-34 of this document.

IV. CONCLUDING COMMENTS

139. As the above comments demonstrate, rather than address specifically many of the important concerns raised by the experts about the EC's evaluation of the safety of the hormones, the EC has chosen instead to attempt to create confusion about these issues. It has done so by presenting the responses of experts in a misleading and flawed manner; it has done so by misrepresenting the meaning of much of the scientific evidence and international guidance documents; and it has done so by attacking the professionalism and objectivity of the experts and the Secretariats of the international organisations.

140. Canada is confident, however, that the Panel will see through these efforts and will keep the focus on the real issues, and on the legitimate scientific and technical material, on which it needs advice to decide this case. Ultimately, on the basis of the substance of the responses from the experts and the lack of substance in the comments by the EC, Canada is confident that the experts have provided sufficient advice to allow the Panel to conclude that the EC's bans are not justified by the scientific evidence.
