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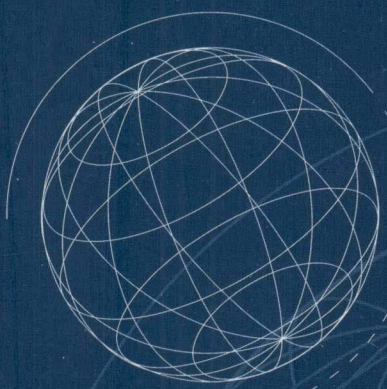

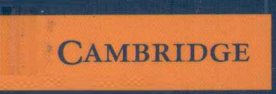

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* This volume contains Annexes F and G to the Report of the Panel.. Annexes A to E of this Report to be found in volume DSR 2008:XII.

ANNEX G

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WITH SCIENTIFIC EXPERTS ON 27-28 SEPTEMBER 2006

ANNEX F-1

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

(30 June 2006)

A. General Definitions

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

EC Comments

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

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

EC Comments

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

B. Risk Assessment Techniques

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

EC Comments

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

Moreover, *Dr. Boisseau's* statement that "*the situation is similar in the European Union*" and that "*The CVMP has assessed all the pharmacologically active substances used in veterinary medecine without any written guideline about risk assessment*" is wrong. It is not the CVMP (Committee on veterinary medicinal products) which is responsible for these hormones when administered for animal growth promotion, but it has been the SCVPH (scientific committee on veterinary measures relating to public health). This latter Committee, and the Euro-

pean 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 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.

[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.

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

EC Comments

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

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

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

EC Comments

The European Communities does not understand the relevance of this question for the purposes of these disputes and the corresponding replies of *Dr. Boisseau* and *Dr. Boobis*. This type of formal distinction between the various components of risk assessment are not mentioned in the *SPS Agreement* and they are clearly not legally binding, since they are not risk "assessment techniques" in the sense of Article 5.1 of the *SPS Agreement*. Moreover, as the Appellate Body has held in the *Hormones* case (at para. 181), to the extent these distinctions are used "to

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

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

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

EC Comments

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

The European Communities notes, however, that there are basic flaws in the replies of both *Dr. Boisseau* and *Dr. Boobis*. Indeed, the accumulation of so much new peer-reviewed evidence since 1999 establishes clearly that oestradiol-17β is a direct carcinogen and does not act only through hormonal receptors. In addition to the peer-reviewed studies mentioned in the 1999, 2000 and 2002 EC risk assessments, it would be appropriate to refer also to the work of Hari K. Bhat, Gloria Calaf, Tom K. Hei, Theresa Loya, and Jaydutt V. Vadgama: *Critical role of oxidative stress in estrogen-induced carcinogenesis*, published in the Proceedings of the National Academy of Sciences, Vol. 100 (2003) 3913-3918,

demonstrating the necessary role of catechols of estradiol or other catechols (2/4-hydroxy-estradiol-alpha produced from estradiol-alpha, menadione) in induction of oxidative stress to induce tumors in the hamster kidney carcinogenesis model. See also the two papers by J. Russo and his co-workers: *17β-Estradiol is carcinogenic in human breast epithelial cells*, and *Estrogen and its metabolites are carcinogenic agents in human breast epithelial cells*, published in the Journal of Steroid Biochemistry & Molecular Biology, vol. 80 (2002) 149-162 and vol. 87 (2003) 1-25, respectively.

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

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

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

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

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

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

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

EC Comments

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

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

Q9. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data

base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

EC Comments

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

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

EC Comments

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

identified risks to human and animal health from the use of these hormones for growth promotion by far exceed any potential benefits.

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

EC Comments

The European Communities agrees with the statement by *Dr. Cogliano*. The statements by *Dr. Boisseau* and *Dr. Boobis* are simply contrary to the findings of the Appellate Body in the 1998 *Hormones* case, where it held that a qualitative risk assessment is equally acceptable under the SPS Agreement and that it does not require the same type of analysis as a quantitative risk assessment. More generally, the issue of whether a threshold model or a non-threshold model is used is critical in determining risk. The literature on no-threshold cited above, in addition to the no-threshold models used for example for PCBs and dioxin, are more appropriate than the current procedures applied by JECFA. For instance, endogenous estrogens are active at inducing some responses in most, if not all, age and population groups. Additivity of exposure to endogenous and exogenous hormones will necessarily result in increased risk at any exogenous dose, no matter how low. Interestingly, the US EPA uses no-threshold models for non-genotoxic chemicals, such as dioxins and PCBs, due to a combination of very long half-lives and activity at very low doses. The European Communities submits that consumption of hormone-treated beef at regular intervals will provide continual or intermittent exposure of estradiol and other growth hormones and thus increase risk and undermine its high level of health protection from these substances.

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

EC Comments

The European Communities disagrees with the statements by *Dr. Boisseau* and *Dr. Boobis* because of their extremely narrow understanding of the concept of scientific uncertainty. They both consider that scientific uncertainty is adequately addressed by JECFA when applying the so-called safety factors. There is however now almost universal agreement that this approach is not scientifically correct. A state of uncertainty may result from a number of factors, such as lack, incomplete or contradictory data. It is not the quantity but the quality of the data that is important. It is possible that an issue that was thought to be scientifically

clear to become uncertain as more data become available. When scientific uncertainty is understood in this sense, this cannot be tackled with the application of so-called safety factors or margins, especially for countries that wish to apply a high level of health protection. For example, the genotoxic and carcinogenic potential of oestradiol-17β cannot be adequately addressed by the safety factors applied by JECFA, because the underlying scientific uncertainty about the mechanisms causing cancer are not amenable to quantification so as to be adequately addressed by the safety factors (there is always the risk of under-inclusion). Another example is that when JECFA evaluated the three natural hormones in 1988 and in 1999 and decide not to set a ADI and a MRL, it based its evaluation concerning endogenous production of these hormones by prepubertal children on very old data from 1974 (citing the paper by Angsusingha K. et al: *Unconjugated estrone, estradiol, and FSH and LH in prepubertal and pubertal males and females*, Journal of Clinical Endocrinology and Metabolism, 39: 63-68 (1974), as reported in the 32nd report of JECFA published in the WHO technical report series no 763, page 32). However, the data reported by Angsusingha et al. are no longer valid in view of the more recent findings with more accurate detection and measurement tools available (see the discussion in paras. 121-122 of the EC 2nd written submission in the US panel and the references thereto to the papers by Klein and Klein and by Anderson and Skakkebaek of 1994, 1999 and 2005, respectively).

It follows from the above that the statement by *Dr. Boisseau* that "for the three natural hormones, oestradiol-17β, progesterone and testosterone, JECFA has decided that the margin of safety deriving from the values of the established ADIs and from a maximum estimated intake of residue was such that it was not necessary to set up MRLs" is plainly wrong. His statement that the European Communities "did not consider any scientific uncertainty" is also false, because a careful reading of the 1999 risk assessment by the SCVPH shows that the reasons for which that scientific committee considered that oestradiol-17β is a proven carcinogen and that the uncertainty regarding the other five hormones (resulting from the lack of data or the presence of contradictory data) are properly explained and taken into account.

Dr. Boobis also made the equally false statement that: "... the EC assessment of the hormones did not go as far as including some of the considerations for uncertainty used by JECFA because of the conclusion that there was insufficient information to determine whether there was a threshold for the carcinogenic effects. However, for some of the compounds this was based on the results of a small number of non-standard tests of genotoxicity, with equivocal of very weak responses. It is not clear whether the EC applied *a weight of evidence approach* to evaluating the genotoxicity of all of the compounds, taking account the totality of the available data, as was the case by JECFA." Indeed, the three risk assessments of 1999, 2000 and 2002 by the SCVPH did consider the totality of the available data. In fact, *Dr. Boobis'* reply does not discusses at all that since 2002, the US authorities concluded that "steroidal estrogens are known to be human carcinogens based on *sufficient evidence of carcinogenicity in humans*, which